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# A Background for Biological Studies with Radioiodine

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PEOPLE WHO MAKE HISTORY, it is said, do not have the time to read it. Nevertheless, a little perspective is a good thing in assessing the value of one's work and in indicating which experiments it is important to pursue. This is particularly true of thyroid physiology because of the rapid speed with which studies involving radioactive iodine have progressed. For instance, my monograph published in 1940 (*21*) includes this statement:

> *Radiation Therapy with Radioactive Iodine.* It has been suggested by a number of investigators that in thyroid hyperplasia and neoplasia it might be possible to treat the disease with iodine, which, being radioactive, would be trapped in the thyroid tissue and would disintegrate there close to the site of the proliferating cells. . . .

It is interesting that this pipe dream, which seemed on the edge of the fantastic at the turn of the present decade, is now rapidly coming true.

*Correlation with the past.* Anyone familiar with investigations in iodine over a period of years becomes impressed by the fact that often the left hand doth not know what the right hand doeth. An illustration is the discovery of iodine, nearly one hundred and forty years ago. During the Napoleonic Wars the emperor was short of nitre with which to make gun powder, and his government subsidized a lot of little people known as *salpetriers* whose business it was to produce saltpeter. This they made from potash and later from kelp or a seaweed which they called *le varech* in the French vernacular. In 1811, a little manufacturer named Courtois discovered (*6*) that there was something in the liquors derived from his seaweed ash which corroded the copper lining of the vats. Out of this industrial problem came the isolation of a purple substance which the eminent French chemist Gay-Lussac (*8*) called iodine, from the Greek word ἰώδης which means *violet-like.*

By 1820 the Swiss physician Coindet (*5*) had published his classic paper on "*Découverte d'un nouveau remède contre le goître.*" This remedy soon became so popular that in the French Midi legislation was passed prohibiting the indiscriminate use of the material. Everybody knew that iodine, which came from seaweed, was a remedy against goiter. Nevertheless, when Baumann (*1*) in 1895 published his classic paper "*Über das Normale Vorkommen von Jod im Thierkörper,*" he said, "*Als ich diese Beobachtung zuerst machte, glaubte ich an alles Andere eher, als dass Jod meiner Substanz angehöre*" (When first I made this observation, nothing was further from my mind, than that iodine was connected with my material).

*Physical biology vs. biological physics.* Speaking with nuclear physicists, biophysicists, clinicians, and various people associated through a common interest in radioiodine, one cannot help being impressed by the fact that a comprehensive view of the problem often would greatly assist their work. The physicist, for example, tends to imagine a human body built up of relays of electric bulbs, wire springs, and steel supports. He evolves theories about this imaginary robot which do not really fit the circumstances of flesh and blood. The clinician, on the other hand, is often just as remiss in his naive way of applying physical tools to a tracer problem. One of the important consequences of the symposia that are frequently held today on biological radioactivity is the opportunity they present for a meeting of minds reared under variegated disciplines.

*Questions to be asked and answered.* An important question that I hope will be brought out in modern investigations is the question of the sweet reasonableness of the results. In other words, how do the data newly presented harmonize with the old facts established by classical chemical methods? In a recent review (*24*) I have attempted to interpret in physiologic terms some of the data on radioactivity now in the literature. Unfortunately, a good many findings are entirely empiric and have no obvious physiologic meaning. In part this is due to the fact that the data on radioactivity have not been integrated with a supportive program of biochemical study. Furthermore, in part the data derived by isotope studies have been confused by technical problems.

This betrayal of the scientist by his armamentarium is no new problem. About 1850, for example, the French scientist Chatin developed a micromethod for measuring iodine. He applied it in a comprehensive study of the waters of the various valleys of the Rhone, the Seine, and other rivers of France. Out of this work he drew the surprisingly clear statement

(*4*) that the principal cause of goiter and cretinism was an insufficiency of iodine. Moreover, he went on to say that it would be a simple matter to reinforce the deficient sources of water supply with mineralized solutions of iodide (*3*). His fellow scientists tried to apply his method and failed. Finally, the French Academy surveyed these results and concluded that Chatin's work was not tenable. The poor man ended his career in disappointment and frustration; and the world remained indifferent to this important etiological factor in goiter until in rather recent decades the work of Marine (*14*), McClendon (*15*) and others eminently confirmed Chatin's hypothesis.

Similarly one finds today that, because of the inadequacy of biochemical and radioactive techniques, our modern scientists frequently disavow conclusions which are plainly true in the light of data established by the older classical methods.

*The integration of older observations with modern findings.* Chatin's contemporaries laid too much emphasis upon negative technical findings. In so doing they ignored a train of independent observations covering a span of 17 centuries. I can mention only a few of these. In the first century A.D., Pliny the Elder (*18*) noted that goiter occurred in certain localities and stated that the waters of these resembled the land. "*Tales sunt aquae quales terrae, per quas fluunt.*" In medieval times sponge had been used to treat goiter (*26*), and later had been incorporated in the "Coventry" treatment used in 18th century England (*27*). In Renaissance times Michelangelo (*16*) complained to his friend Giovanni da Pistoja that he had grown a goiter while painting in the Sistine Chapel—just as a cat in Lombardy might:

> I'ho già fatto un gozzo in questo stento,
> come fa l'acqua a' gatti in Lombardia,
> ovver d'altro paese che si sia,
> ch' a forza il ventre appicca sotto il mento.
>
> I've grown a goiter by dwelling in this den—
> As cats from stagnant streams in Lombardy,
> Or in what other land they hap to be—
> Which drives the belly close beneath the chin.

In 1812 Courtois (*6*) had discovered iodine in seaweed, and in 1809 the London Medical Dictionary (*17*) had recommended sea water to treat goiter. One wonders, now, how the leading French scientists dared to discredit Chatin's conclusions. Of course, hindsight is ever more lucid that foresight and it is all too easy to scoff in retrospect. As he picks up his beautiful new tool, however, it is well for the modern biologist to remind himself how subtly and completely a fascination for gadgets can betray sound sense.

*Evaluation of tools and methods.* Part of the difficulty lies in a misplaced confidence in one's technique, or perhaps a failure to appraise the limitations of methodology. Again, history supplies an illustration. In 1848, King (*10*) at Guy's Hospital in London had hypothecated the existence of an internal secretion derived from the thyroid:

> . . . we may one day be able to shew, that a particular material principle is slowly formed and partially kept in reserve; and that this principle is also supplementary when poured into the descending cava, to important subsequent functions in the course of circulation.

Moreover about 1883, the rival Swiss surgeons Kocher of Berne and Reverdin of Geneva had agreed (*11, 20*) that the more nearly complete their thyroidectomy, the worse for the patient ultimately. After Sir William Gull (*9*) had described the widespread tissue changes in human myxedema and Fox (*7*) and Mackenzie (*13*) had demonstrated the reversal of these changes by the feeding of thyroid, Baumann (*1*) showed that the essential substance "thyroidin" contained iodine. It should have been obvious that an iodine-containing hormone normally circulates in the blood stream. Nevertheless, as late as 1914 it was believed (*2*) that the normal plasma contained no iodine in organic combination. The discrepancy was resolved only after improved techniques had been devised. Similarly, in the present decade the earlier publications on radioactive iodine frequently constituted pharmacologic rather than physiologic endeavors; because too much carrier (inert) iodide accompanied the so-called "tracer." Therefore, we must endeavor to bring out the answer to the question: How do these data harmonize with the established knowledge of thyroid physiology and iodine metabolism already developed painstakingly by classical methods of biochemistry?

*Newer knowledge.* We must also ask what new concepts have evolved from the use of radioactive iodine that were not established earlier. Obviously this new tool—perhaps the most important scientific weapon since the discovery of the microscope—provides the opportunity for a kaleidoscopic or cinematographic picture of metabolic events. By making repeated observations in a single animal or man, one can obtain a picture which formerly would have required the sacrifice of whole series of test animals. Nevertheless, it is a little disappointing to find some modern isotope-minded physiologists content with developing a series of data and proclaiming conclusions which are already well established in the literature of thirty years ago. Granted that the older data were built of painstaking analyses on single animals and the composite picture which had to be drawn therefrom; yet the final concepts—the heart of the problem—often have already been resolved by older techniques.

This problem of rediscovering what was long since established is not new. In October 1863 the eminent French clinician Trousseau (*25*) inadvertently gave a patient with exophthalmic goiter some tincture of iodine when he meant to write tincture of digitalis on the prescription blank. He did this because he knew subconsciously that iodine was traditionally a bad drug for these people. When the patient returned to his office, however, she was much improved. Discovering his mistake, the physician changed to tincture of digitalis and the patient rapidly became worse. In short, before the time of the American War between the States it had been demonstrated clearly that iodine was a good remedy in hyperthyroidism. Nevertheless, when Henry Plummer (*19*) in the third decade of this century emphasized the use of iodine in such cases, the world hailed this as a novel approach. Circumstances change but the general pattern is the same. Men do over and over again what their predecessors did two generations ahead of them because the train of history is lost.

One of the most important things which the isotope technique can give us, besides localization of the material anatomically, is the indication of its rate of metabolic turnover. Such measurements, however, cannot be established through isotopes alone. In order to establish turnover rates it is usually necessary to have simultaneous measurements of both stable isotope and tracer. It is surprising how many physiologists, biochemists, and clinical investigators still rely solely on determining radioactivity, without supportive biochemical analyses of the classical type.

*Combined chemical and physical approaches.* There is a tendency in present-day tracer studies to rely on biophysical measurements alone, without accompanying chemical identification (either qualitative or quantitative) of the substance under observation. For instance, the thyroid gland normally contains iodine in three chemical forms; but rarely are they separated before measurements of radioactivity are made (*12*). Moreover, the fact is frequently overlooked that in order to interpret measurements of radioactivity, simultaneous measurements must be made of the inert iodine present. In other words, it is frequently necessary to know the *specific radioactivity* of the chemical substance or fraction under study. Consider the blood plasma of the normal rat, with a steady concentration of "hormonal" iodine $H_o$ at about 2.5 micrograms percent. If one is to estimate the turnover rate of this hormone by administering radioiodide, one must combine data on radioactivity with microchemical analyses because the hormonal concentration represents a dynamic equilibrium (*22*). As fast as a little new radioactive hormone is formed, part of it is metabolized together with the previously extant hormone. This relationship is represented by the equation

$$\frac{dH}{dt}\left(1-\frac{L}{H_o}\right)=\frac{dL}{dt},$$

where $H$ is the newly formed hormone and $L$ the labeled hormone unexpended. At any given moment $L$ can be evaluated from measurements of $A$, the radioactivity observed, and from $\sigma$, the specific radioactivity of the body's reserve of iodide. As a first approximation, these can be described by the following equations:

$$\frac{-d\log\sigma}{dt}=k,$$

$$\frac{dL}{dt}=\frac{dA}{\sigma dt}=\frac{1}{K_o}\cdot e^{k_1 t}\frac{dA}{dt}.$$

Once $L$ has been evaluated, the amount of newly made hormone can be calculated easily because

$$H_{t_o}=-2.5\,In\left(1-\frac{L_{t_o}}{2.5}\right).$$

The ultimate solution for turnover rate, therefore, involves some sort of multiple integration. Without this mathematical approach much of the work which has appeared in the last few years cannot be interpreted physiologically (*23*). In general, for work with biological systems one cannot be content with isolated physical measurements presented on an empirical basis.

At this juncture, therefore, it is well to stop and think in terms of our accumulated knowledge of iodine metabolism and of thyroid physiology. Let us ferret out those new developments and new concepts for which the use of radioiodine is directly responsible. Let us inquire carefully into technical problems and means of solving them; but let us not be so diverted with gadgets that we forget the purposes which these tools might serve. Let us remember that biophysical methods must be adapted to the organism rather than the organism warped to fit oversimplified physical theory. If we bear these points in mind, we shall be able to bring out the answers to our chief questions, namely: 1) How has radioiodine improved our knowledge of iodine metabolism and of the physiology and the therapy of the thyroid? and 2) How do the results harmonize with past experience? If we understand clearly the answers to these questions it will be obvious what work must be done to make progress along modern biological lines.

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# Standardization of Radioactive Iodine

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THE TECHNIQUES AND INSTRUMENTATION of standardization that are to be described here are those available generally in laboratories equipped for work with radioactive materials in biology and medicine. Problems that can be solved by specialized and more complicated methods in a purely physical laboratory will be discussed only in a general way; however, such measurements as can and should be performed by every user of radioactive materials, especially I–131, will be presented in more detail.

The standardization of a physical object involves first of all a description of the measurement procedure and a definition of the unit to be used. The two are, however, not necessarily independent of each other; and we usually are free to select more than one procedure and unit.

Let us consider a piece of steel. We can standardize it by weighing, and the unit which we will assign to it by this procedure may be the kilogram. As is true of every good physical unit, there are several well-known measurement procedures for comparing our piece of steel to the physically permanent standard kilogram. The "weight" is an adequate standardization result if we want to use the piece of steel as ballast in a ship. Should we want it for casting, however, weight will not be the information required; we shall need its volume, expressed, let us say, in ml. To measure this directly is rather more complicated than weighing; we should not be permitted to use density, since "density" implies that a volume measurement and weighing have been performed on the identical steel at least once previously. If we plan to use the piece of steel as an armor plate, we shall need a different standardization, its thickness in cm, which can be easily measured by a micrometer. The situation will become more involved if we are to use the steel as a gamma-ray absorber. The micrometer, which gives the thickness in cm, will be very useful as long as we use the same steel alloy. But if we use different steel alloys, or even different materials, we find that the simple absorption equation is complicated by a coefficient that is characteristic for every material and varies widely. We know from our experience that the variation of this coefficient is reduced by at least one order of magnitude if we standardize the thickness of absorbing materials in $g/cm^2$ instead of cm. Such standardization involves more complicated measurements than the simple use of a micrometer. Yet this is what we do, for reasons familiar to us all.

The purpose of this example is to recall the multitude of possible standardizations on the same physical object and to show 1) how availability and simplicity of measurement procedures may determine the selection of units, and 2) that, depending on the ultimate use and application of the information supplied by standardization, one system of units may be exchanged for another, for simplicity and convenience.

In working with short-lived radioactive isotopes, a gravimetric unit for standardization is practically im-

possible. One hundred μg of I–131, the smallest amount that can be weighed with reasonable precision, has, after filtration of beta radiation, a gamma radiation equal in ionization to about 15 g of radium. Such large amounts were undreamed of only a few years ago, and their handling is too hazardous for routine procedures. We had to work with very minute quantities, which could be detected and measured with the G-M tube.

The G-M tube indicates single radiation events associated with nuclear disintegrations. It seems natural, therefore, that, at a time when only small quantities of radioactive isotopes were available, most easily detected and measured by the G-M tube, a unit based on the disintegration rate was proposed and came into general use. This unit was derived from the curie—the amount of any nuclide of the radium family in secular equilibrium with 1 g of radium. It is hence derived from a gravimetric unit.

In selecting a disintegration rate unit for radioactive isotopes, it appeared natural at first to tie it in with radium measurements and to use as the unit a disintegration rate equal to the disintegration rate of one curie of radium. The disintegration rate of radium, however, is not known to better than about ½% accuracy. A number close to the experimental value was chosen, therefore, and was used in the definition: 1 millicurie of a radioactive isotope is the amount in which, at the time of measurement, 37 million disintegrations occur per second.

One of the objections raised against the use of the disintegration rate mc was the possibility of confusion with the radium mc. Condon and Curtiss have proposed the rutherford (rd), defined as 1 million disintegrations per second. I do not feel that the possibility of confusion is sufficiently serious to warrant the introduction of a new name and unit. Any standardization result always reads: "$x$ units of $y$ isotope." Whenever $y$ is not radium, we know that disintegration rate is meant. It is scarcely worth while to differentiate the disintegration rate mc by a prefix as "isotope mc." The numerical simplicity of the "rutherford" is an even slighter advantage.

After this lengthy introduction we can approach our proper subject: standardization of radioiodine. Before we discuss how we can use the mc unit, let us look at Fig. 1, summarizing the results of standardizations performed in 70 different laboratories in this country on samples of equal content of I–131 (third intercomparison by the National Bureau of Standards). This offers quite a dismal picture. The standard deviation is about 30%; the range is from 43 to 180, about 1:4, almost an order of magnitude.

Obviously, standardization is not a simple procedure. Yet it is an extremely important one. If a worker at the upper end of the frequency plot reports a certain dosage for treatment of a given disease, and a worker at the lower end makes use of this dosage

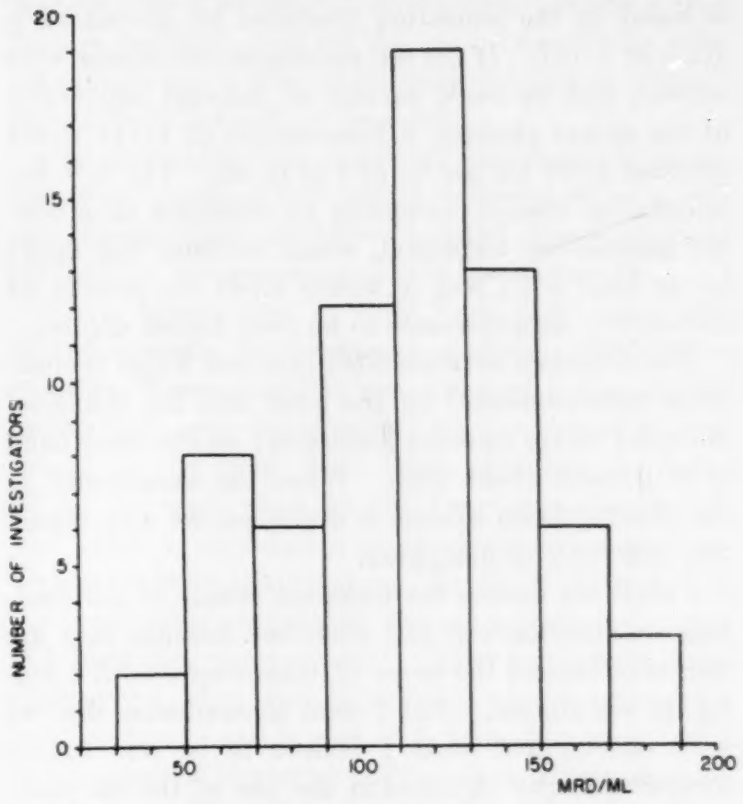


FIG. 1. Frequency distribution plot of standardization results by 70 laboratories (third intercomparison conducted by the National Bureau of Standards).

information, he will give four times the effective dose, will possibly exceed the therapeutic latitude, and will get deleterious results (permanent hypothyroidism, for instance, in treatment of Graves' disease).

We can make some fairly good guesses at the reasons for this wide spread.

There are actually several factors involved, and for purposes of discussion we may differentiate three groups among the 70 laboratories: 1) those making their own primary measurements; 2) those comparing the counts from a standardization sample of a long-lived radioactive isotope with the counts from the I–131 sample to be standardized; and 3) those calibrating their measurement equipment with a sample of I–131 standardized by a laboratory of group 1 or 2.

The spread of the NBS intercomparison is obviously due to the discrepancies in the determinations of groups 1 and 2, on which are superimposed the errors of group 3. The discrepancies in the results of the workers in group 1 mirror the actual difficulties of absolute standardization in millicuries. Theoretically, the best and apparently the most direct method of disintegration rate determination is that of coincidence counting. However, this has the serious disadvantage that its correct use presupposes knowledge of the exact disintegration scheme. The disintegration scheme

of I–131 that we had formerly assumed to be correct is now in doubt. This uncertainty makes the results of coincidence measurements doubtful.

A second method of absolute standardization in mc is based on the ionization produced by gamma radiation of I–131. If the old disintegration scheme were correct, and we could assume no internal conversion of the 80-kev photons, a 1-mc-sample of I–131 would produce 0.265 mr per hr at 1 m in air. The new disintegration scheme, accepting an incidence of a 650-kev gamma-ray transition, would increase this figure by at least 5%; and it would affect the results of coincidence measurements to an even higher degree.

The difference between NBS and Oak Ridge (coincidence measurements) on one hand, and the Memorial Hospital values (gamma ionization) on the other hand is at present about 20%. When the uncertainty in the disintegration scheme is overcome, we may expect this difference to disappear.

I shall not discuss the technical details of the absolute standardizations just described because they are normally beyond the scope of laboratories with a biological orientation. But I want to emphasize that we have encountered what I believe to be one fundamental difficulty involved in the use of the mc unit: in order to use it in the standardization of an isotope sample we need a considerable amount of information about the isotope's nuclear behavior, which we do not have for most isotopes.

Workers of group 2 have new difficulties, due to the different energies of the radiations of the long-lived reference standard and of I–131. The beta energy of RaD + E standard, for instance, is much higher than the beta energy of I–131. This brings about not only an increased error in the extrapolation for zero absorber, but introduces errors due to the difference in counter efficiency at different energies, and also differences in scattering. All this necessitates complicated corrections, with the possibility of a considerable cumulative error.

There is, at least theoretically, a solution for the method of group 2: the preparation of a long-lived isotope standard with a radiation of type and energy close to that of I–131. A 3.5-year-half-life isotope of thalium (Tl–206) disintegrates by beta emission of 0.87 Mev, which is close to the I–131 beta energy of 0.687 Mev. I–131 samples, compared with such a standard using suitable filters for gamma background correction, may give values requiring only small correction factors for the characteristics of the G-M tube and the material and geometry of the shelf setup. The ideal solution would be a mixture of long-lived isotopes, all of which have the same half-life, and which emit beta- and gamma-rays iso-energetic with I–131; however, such a mixture does not appear feasible.

An essential advantage of group 2 methods, apart from the difficulties and uncertainties which have been discussed, is the availability of a permanent reference standard which insures against short or long term fluctuations in the sensitivity of measuring equipment and against losing the calibration when replacing or changing such equipment.

We come now to group 3, which is our proper domain: standardization by use of instruments calibrated against a "known" I–131 sample. We have to keep in mind, of course, the errors and uncertainties in the measurements of group 1 or 2, who have supplied the sample.

As a first example, we may take the simplest situation which occurs in tracer work: we want to measure the excretion of I–131 after oral administration of a tracer dose. We will keep an aliquot of the administered solution as reference sample, and measure the excretion in urine against the known standard. This will not only eliminate automatically the decay factor, but it will also take care of long term instability of our G-M setup. There will be one very important precaution to be observed: there must be complete identity in the preparation and handling, and in the physical and geometrical counting setups of the reference standard and the measured sample. If we use dried samples in order to obtain maximum sensitivity, we risk variations not only in self-absorption but also in loss of I–131 from the two samples, due to differences in drying, pH, etc., between the standard and the urine samples. Loss of iodine is a serious source of error in working with dried samples. I suspect, for instance, that the lower values in Fig. 1 (intercomparison by the National Bureau of Standards) is due to the use of dried samples with the concomitant loss of active material.

It is simpler to eliminate this error by the use of liquid samples. G-M tube setups with adequate sensitivity have been devised for this work—concentric gamma counters (Marinelli), and mixed beta and gamma counting, using liquid samples with thin glass wall cylindrical G-M tubes or with bell type counters of sufficiently large diameter. When using liquid samples, the danger of losing some iodine is reduced, but not eliminated. Here the main factor is pH. In the preparation of samples from the alkaline I–131 solution supplied by Oak Ridge, we found it best to dilute with distilled water only, checking with indicator paper.

The usefulness of a known standardized I–131 sample for direct comparison ends in a few weeks because of radioactive decay. We might attempt to maintain

the direct comparison method by preparing a secondary, tertiary, etc., 1–131 standard sample. But the errors will accumulate and in a few months we would expect a considerable drift from the original standard. We would, therefore, prefer to obtain a *permanent calibration* of our equipment on the basis of the original known sample. But the G-M tubes, which we hold in such a high esteem because of their sensitivity, are rather unreliable as far as the permanence of their calibration goes. Their counting efficiency is subject to many fluctuations, due to such factors as temperature, air pressure, and aging. To some extent, these

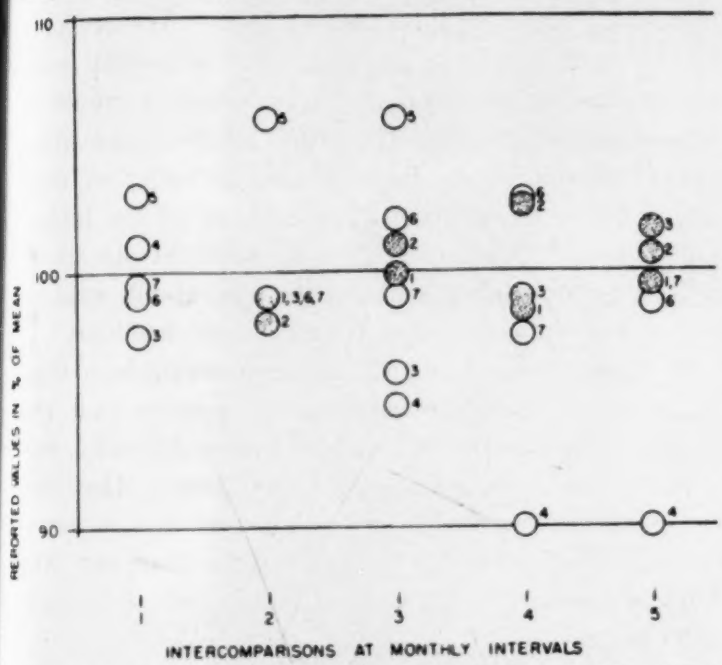


FIG. 2. Results of standardization by seven New York laboratories. Plain circles, G-M tube measurements; stippled circles, ionization chamber measurements.

fluctuations can be taken into account by frequent check (several times daily) against a radium source.

When using such radium check, several points must be considered. Radium buttons of luminescent paint are unreliable because of the erratic loss of radon. Glass ampules with radium chloride solution, supplied by the NBS are adequate, but they are inconvenient to handle, and fragile. I have prepared sources with a few micrograms of radium by sealing radium paint in glass tubes and mounting the tubes in metal containers ¼ inch in diameter and 1 inch long. They are convenient to handle, since it is easy to place them in a reproducible position with respect to the counter by drilling a ¼-inch hole somewhere in the counter setup. The sources have proved satisfactory in our own and in two other laboratories.

The use of a radium check improves the constancy of the G-M tube calibration, but does not make it perfect or permanent; there is no reason to assume that the counting efficiency ratio of the G-M tube between the hard gamma radiation of radium and the softer gamma radiation and beta radiation of I–131 remains constant throughout the useful tube life. Using a radium check, one may expect a steady drift of the calibration. The use of a radium sample as a check is therefore an improvement, especially for short periods; but it is not a final solution. When a G-M tube is replaced, even by the same type of the same manufacturer, a new calibration against a "fresh" known I–131 sample is required.

Fig. 2 illustrates the degree of consistency in standardization practice that can be achieved between several independent laboratories using this method of calibrating equipment against a known sample.

Seven laboratories in New York City[1] have conducted monthly intercomparisons during the last five months. The radioiodine samples used in the original calibrations were standardized by the Memorial Hospital. In the third NBS intercomparison, we were all on the main peak of the frequency distribution plot (Fig. 1) and had a standard deviation of 3.5% among the seven laboratories. In Fig. 2, summarizing our local intercomparisons, the open circles represent G-M counting measurements. After the second intercomparison, Memorial Hospital corrected absorption extrapolations, and is now 10% below the mean based on the original Memorial values. The standardization results are within 5% of the mean. I believe, however, that without future recalibration these G-M values will drift apart.

I feel convinced that the solution of our problem is the replacement of the highly sensitive and somewhat temperamental G-M tube by a less sensitive but more rugged and reliable instrument for purposes of standardization, such as the ionization chamber.

The required sensitivity is dictated today, not by the available amounts of once scarce isotopes, but by health hazards in handling. Since it is relatively safe to handle a few hundred μc of I–131, the great sensitivity of the G-M tube is not required. The sensitivity of an ordinary thimble chamber, however, is not great enough.

Carl B. Braestrup has designed an ionization chamber of suitable sensitivity for use with I–131, which is illustrated in Fig. 3. This chamber can be used with any conventional electrometer of the Victoreen type. The I–131 sample is introduced into the chamber enclosed in a glass test tube. Correction factors for difference in volume of the sample are less than ½% up to 6 ml. The sensitivity is such that about 400 μc of

[1] Columbia University, Radiological Research Laboratory, G. Failla (ionization measurements) and E. Quimby (G-M counting); Memorial Hospital and Sloan Kettering Institute, L. Marinelli; Montefiore Hospital, E. Oshry; Mount Sinai Hospital, S. Feitelberg; New York City Department of Hospitals, C. B. Braestrup; Veterans Administration Hospital, R. Yallow.

I–131 give the optimal discharge of 3/5ths of the Victoreen scale in 10 min.

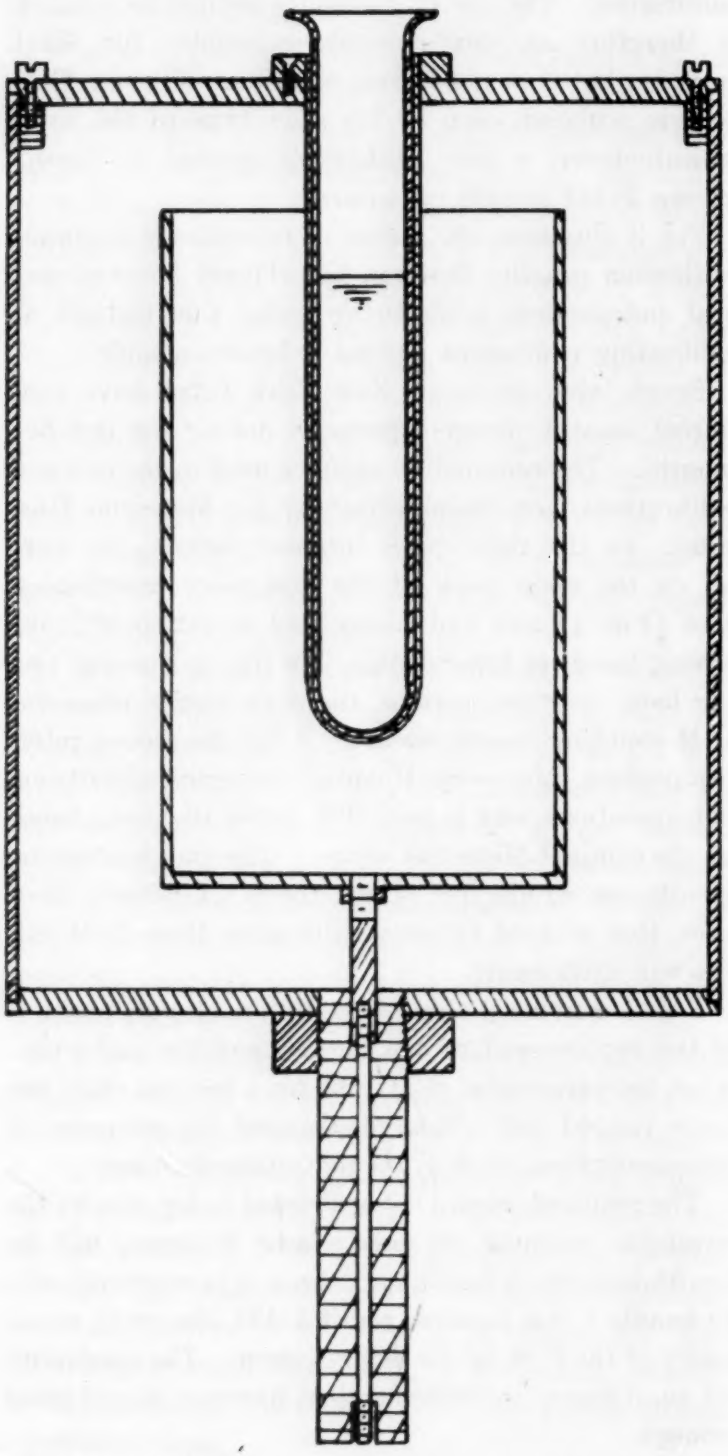

FIG. 3. Ionization chamber for gamma emitting isotopes, designed by Carl B. Braestrup. The chamber is made of brass, outside diameter 4 inches.

Another type of ionization chamber instrument has been designed by Failla; among other advantages it can also be used with pure beta emitters. However, it is rather expensive and not yet available commercially.

The essential advantage of ionization chambers is their simplicity, ruggedness and reproducibility. Once a Braestrup or Failla chamber is calibrated against a known radioiodine sample, it can be relied upon to give reproducible readings. Now the electrometer becomes the course of uncertainty, but we can eliminate this factor by checking against a radium source of 100 to 200 μg, which incidentally also compensates for variations due to air pressure and temperature changes.

The stippled circles in Fig. 2 are results of ionization chamber standardizations. They are within 3% of the mean. Radium checks, which have not been used yet for these measurements, may improve the consistency even further.

What precision in standardization do we need in biological work? The answer lies in the biological factors involved. For instance, the biological information for calculating dosage to the thyroid gland has a probable error of the order of 30%. We certainly do not want to have a physical error of similar magnitude superimposed on this. However, it would be unreasonable to require the errors in the standardization measurements to be less than an order of magnitude below the errors in the estimate of the biological factors. This means that we want the standardizations to be reliable within 3 to 5%, about what we expect in standardization of an X-ray machine.

If I may refer again to the intercomparison work of the New York laboratories, it appears that this precision can be achieved without undue difficulty, particularly when using ionization chambers. However, this pertains to relative and not to absolute measurements. We certainly do not believe that our New York mc comes within 5% of 37 million disintegrations per sec.

What is the ultimate purpose of the standardization information? It is two-fold: 1) to obtain a common denominator among all the workers, so that the experience of one group can be used by others, and so that the experience of all can be pooled in order to arrive at an empirically determined dosage; 2) to link the experience of internal radiation using radioiodine with the employment of other modalities of radiation therapy.

The present state of the art permits the accomplishment of the first purpose. I believe that one of the national agencies concerned with this work should initiate on a national scale a project similar to that undertaken by the New York laboratories at city level. In addition to supplying uniform standardized samples at regular intervals, such a project would also make available critique and advice on standardization practice to workers who find difficulties in achieving reproducible results. For this purpose it is irrelevant what I–131 mc unit is used. It should be possible, within a few months, to reduce the national spread to a standard deviation of at most 5%. We in New York will shift from our somewhat arbitrary but, we believe, consistent and reproducible "New York mc" to any value on which there is such national agreement.

The second purpose is linked with absolute measurements. An arbitrary mc dose does not permit us to use with confidence the factors necessary for calculating energy absorption in tissue (rep). Discrepancies in primary absolute measurements are considerable. We may have to wait until these discrepancies are resolved, and until the disintegration scheme of I-131 is thoroughly established. However, there is another solution. We could take, for instance, the New York mc and measure the energy emitted for such a unit of I–131. If such measurements were available (I believe that they are being made at present), we could calculate dosage in roentgen equivalents, and the mc with its inherent uncertainty would cancel out.

In this connection, I would like to recall to you Failla's suggestion for a unit of radioactive isotopes, which he calls "ruth," for Rutherford: one ruth is the amount of any radioactive isotope that emits ionizing radiation at the rate of one erg per sec. Since I believe that the ionization chamber will replace the G-M tube as a standardization instrument, it seems to me that the disintegration rate unit will lose its usefulness. It is not very practical to use a unit which implies disintegration rate measurements if the actual standardization practice measures the amount of ionization and does not count the number of ionizing events. But this is not the opportunity to recapitulate Failla's arguments, with which I personally agree. The main advantage of the ruth, I think, is that a unit based on energy emission furnishes more directly the information which we, as consumers of atomic energy, ultimately require.

I have attempted to present the material necessary for the evaluation of standardization procedures and for the accomplishment of reproducible comparison measurements. Our main effort in standardization work should be directed toward a uniform standardization, although this may be for the time being on the basis of a standard which is to some extent arbitrary. All of us can contribute to this limited objective.

The question of absolute standardization is the domain of a smaller group. The majority of us will have to wait for their results. But I hope that I may speak for this majority if I define what kind of result we need from absolute measurements: it is a result that will permit us to compute energy absorption of ionizing radiations of radioactive iodine in tissue.

*Based on a paper presented at the Symposium on Radioactive Iodine held at Brookhaven National Laboratory, Upton, New York in July 1948.*

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# Interstellar Polarization, Galactic Magnetic Fields, and Ferromagnetism

Lyman Spitzer, Jr., and John W. Tukey[1]

*Princeton University*

OBSERVATIONS by W. A. Hiltner (*5, 6*) and J. S. Hall (*4*) indicate that starlight becomes plane polarized in its passage through interstellar space. The effect increases with increasing distance, and according to Hall's data amounts to about 5 percent ($= e^{0.05}$) difference in intensity between the two plane-polarized components for a star whose color excess is 0.50 magnitude. Since the color excess is known to be about one-ninth the total absorption (which thus amounts to $(2.512)^{-4.5} = e^{-4.1}$ for such a star), the absorption must vary by somewhat more than one percent with the plane of polarization.

Such polarizing absorption would exist if needle-shaped particles, of dimensions comparable with a wavelength of visible light, were present in interstellar space, and were oriented by some force. The ratio of the scattering cross sections of such needles for the two planes of polarization would be appreciable; according to the theory by R. Gans (*3*), for a small prolate spheroid with a length twice its diameter, this ratio is 2.74 if the refractive index in the spheroid equals 2.5. Thus a relatively small number of needles could produce the observed effect.

Two difficulties seem to stand in the way of this explanation: the origin of the needles and their orientation. If we accept as a working hypothesis: (1) the existence of small ferromagnetic particles, which, existing as individual domains, are intensely magnetic; and (2) the existence of magnetic fields in interstellar space with systematic components as great as $10^{-5}$ gauss; then these difficulties disappear. The first of these suppositions appears reasonable from an exten-

[1] The authors are indebted to Drs. John Turkevitch, John Wheeler, and Eugene P. Wigner for generous and helpful comments.

sion of the theory of J. Oort and H. C. van de Hulst (*8*) on the origin and growth of interstellar grains, while the fields proposed are of the order of those recently postulated by E. Fermi (*2*) in his theory of the origin of cosmic rays.

According to Oort and van de Hulst, the interstellar grains grow by the accretion of atoms and evaporate on mutual impact when two clouds collide. Differences between the different molecules within a grain are not considered in the original form of this theory, but in most collisions the more volatile components must evaporate preferentially, thus concentrating the heavier atoms.

The relative numbers of different atoms other than H inside the grain may be taken as: O—100, C—40, N—40, Fe—10, Si—8, Mg—6, S—6, and others—½ or less. Most of these elements will be chemically bound with H, which is overwhelmingly the most abundant element in interstellar space, or with O. Thus when the grain is heated, most of these elements will go off as volatile hydrogen or oxygen compounds, leaving primarily Fe and Mg atoms and oxides, and some $SiO_2$, some Si going off as $SiH_4$. It is uncertain whether Fe and Mg will be left in the metallic phase, since they may be expected to form oxides by interaction with O or with $H_2O$ before these are lost by evaporation. FeO seems less likely than $Fe_3O_4$ or $Fe_2O_3$, in view of the high relative abundance of O. $Fe_3O_4$ is a well-known ferromagnetic substance, and $Fe_2O_3$, when precipitated from a water solution, tends to form cubic crystals which are ferromagnetic.[2] Magnesium iron spinel, $MgFe_2O_4$, is also known to be ferromagnetic (*9*). Thus, the production of ferromagnetic grains by this process seems likely.

Theory and observation (*1, 7*) both indicate that small ferromagnetic particles, of radius about $10^{-6}$ cm or less, form single domains, uniformly magnetized. For somewhat larger particles the information is less definite, but it would appear that ferromagnetic particles of radius $2 \times 10^{-5}$ cm are likely also to constitute single domains.[3] Furthermore, it is likely that an appreciable number of such particles would stick together on impact and form elongated particles, since the mutual energy involved vastly exceeds the thermal energy. For nearly spherical grains the parallel, end-to-end orientation provides much the larger interaction energy, and is therefore more probable.

Next we consider the orientation of such grains. The energy of orientation of a grain in a magnetic field of strength $H$ is about $HIV$, where the volume $V$ may be taken as $2 \times 10^{-14}$ cm³ for a cylinder $1.5 \times 10^{-5}$ cm in radius and $3 \times 10^{-5}$ cm in length. The intensity of magnetization $I$ is about $10^3$ gauss in a ferromagnetic domain. With $H$ equal to $10^{-5}$ gauss, this orientation energy is $2 \times 10^{-16}$ ergs, as compared with a value of about $10^{-15}$ ergs for $kT$ at 10° absolute, a not unreasonable value inside a dense obscuring cloud. While Fermi's assumed magnetic fields would have different values in different clouds, the average number of clouds in the line of sight to a star 500 parsecs away is only 3 to 4, and the average net $|H|$ perpendicular to the line of sight should be about ½ the rms $H$.

It is evident that production and partial orientation of ferromagnetic grains in interstellar space is at least consistent with present astrophysical theory. Since the indices of refraction for pure $Fe_2O_3$, MgO, and $MgFe_2O_4$ are about 3, 1.7, and 2.3, respectively, such particles would scatter light more effectively than the conventional ice particles discussed by Oort and van de Hulst. Thus the ratio of the number of oriented ferromagnetic needles to the number of unoriented grains of comparable size need be only a small fraction of a percent to explain the polarization observations. Obviously, further observations are needed, and much theoretical work remains to be done, both on the chemistry of the fusion process, and on the subsequent magnetic and optical properties of the resultant grains, before the suggestions presented here can be regarded as more than a working hypothesis. If additional research confirms the present picture, it may become possible to obtain direct experimental evidence on the magnitudes and directions of magnetic fields in interstellar space.

[2] We are indebted to Dr. L. W. McKeehan for this information.

[3] We are indebted to Dr. C. Kittel for this information.

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# TECHNICAL PAPERS

## Effect of Swine Influenza Virus on the Viscosity of the Egg-white Inhibitor of Hemagglutination[1]

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Egg-white (EW) contains a component which is capable of combining with influenza virus and inhibiting the agglutinative reaction of virus with *RBC* (*3, 5–6*). Furthermore, untreated purified swine influenza virus is capable of destroying the EW inhibitor, but suitably heated virus is essentially devoid of such destructive capacity (*7*). Thus far, the destruction of inhibitor by virus, which has aspects of an enzymatic action, has been inferred only from indirect experiments based on the hemagglutination phenomenon. Recently, it has been observed, as described briefly in the present report, that virus exerts a profound effect on the viscosity of solutions of semipurified EW inhibitor.

Semipurified inhibitor preparations were obtained from EW by repeated precipitation at pH 5.7 and extraction of the precipitate with 0.06 M phosphate buffer at pH 7.2 (*8*). Typical extracts, which were 40 to 60 times as active as EW on a nitrogen basis, contained 25 to 150 $\gamma$ N and 50 to 125 $\gamma$ carbohydrate[2] per ml; one preparation, A178 PIII EI, which was 41 times as active as EW, contained 150 $\gamma$ N per ml and 12.5% N on the basis of dry weight. The inhibitor was nondialyizable and gave qualitative tests for protein. The swine influenza virus was a freshly purified preparation, obtained as previously described (*10*), containing 400 $\gamma$ N per ml and characterized by a 50% endpoint infectious unit of $10^{-14.4}$ g N. The viscosity experiments were carried out in capillary viscometers (*9*) at 29.78° C.

The relative viscosity of preparation A178 PIII EI was found to be linear with respect to concentration over the range from 0 to 150 $\gamma$ N per ml and had the value 1.255 at 100 $\gamma$ N per ml. Assuming a density of 1.33 for the viscous component of this preparation, one may calculate a minimal viscosity increment (*4*) of approximately 400, a value considerably greater than that which is obtained with ordinary proteins (*4*). From this result one may infer the presence of a highly asymmetric component.

[1] This work was aided by a grant to Duke University from Lederle Laboratories Inc., Pearl River, N. Y., and by the Dorothy Beard Research Fund.

[2] Determined with the orcinol reagent and calculated as glucose.

The effect of untreated, purified swine influenza virus on the viscosity of inhibitor solutions is shown in Fig. 1. The rate of decrease in viscosity is initially rapid, falling to a low value within a few minutes. The terminal viscosity (after 24 hr) of virus inhibitor mixtures was approximately 1.01, corresponding to a reduction of 80 to 90% in the specific viscosity (relative viscosity −1). This terminal value was essentially independent of the initial virus concentration.

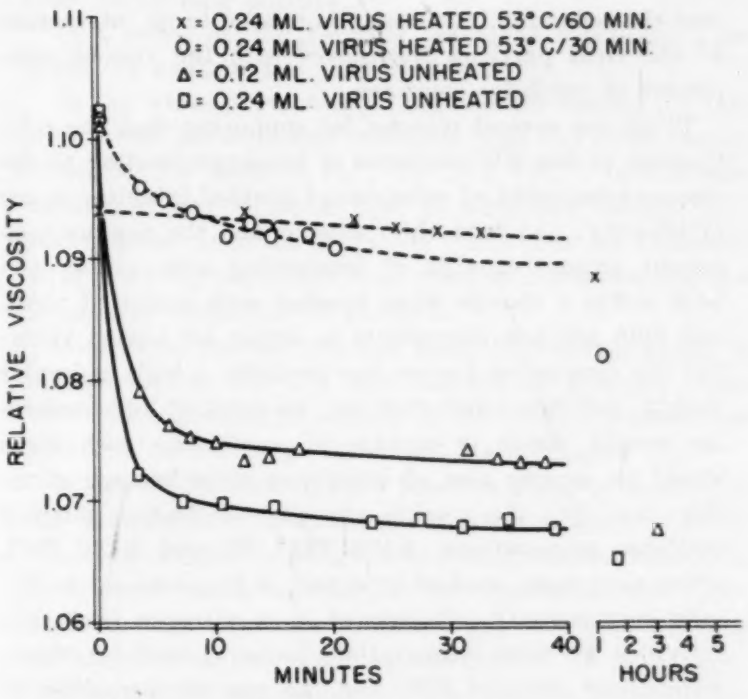


FIG. 1. Effect of heated and unheated purified swine influenza virus on the viscosity of solutions of purified EW inhibitor. The virus preparation contained 200 $\gamma$ N per ml (2.2 mg virus per ml). The volume of virus preparation indicated in the chart was added to 10 ml of the inhibitor preparation A180 PEI containing 30 $\gamma$ N per ml.

In an experiment of a different sort, 0.24 ml virus at a concentration of 200 $\gamma$ N, or 2,200 $\gamma$ virus per ml, was mixed with 10 ml inhibitor solution containing 30 $\gamma$ N per ml with a relative viscosity of 1.0815, and the reaction was followed in the viscometer. After 25 min, when the relative viscosity was 1.0685 and was changing slowly, 5 ml reaction mixture was mixed with 5 ml fresh inhibitor solution. This process was repeated three more times. With each addition of fresh inhibitor there occurred a burst of activity as manifested in a rapid initial fall in viscosity. While it is difficult to interpret the results precisely at the present time, the experiment gave no evidence of saturation of the viscosity reducing capacity of the virus preparation. The activity of the fresh inhibitor solution was such that a quantity of 10 ml would have been capable of inhibiting the hemagglutinating activity of approximately 30 mg of virus heated 30 min at 53° C in concentration of 1 $\gamma$ N per ml.

Fig. 1 shows also that heating the purified virus preparation for different periods at 53° C progressively reduces the capacity of the virus to cause a decrease in viscosity. These results with heated virus have a correlate in the reduction of the inhibitor destroying capacity of virus consequent to heating (*7*).

Studies of the effect of convalescent antiswine influenza swine serum showed that a quantity of serum capable of neutralizing completely the hemagglutinative activity of the virus prevented completely the typical effect of virus on inhibitor viscosity. The same amount of normal swine serum was somewhat less effective. The dependence of the rate of viscosity reduction on virus concentration and on the state of the virus, i.e., whether the virus was heated or not heated, as well as the absence of viscosity changes in the presence of immune serum, suggests that the reduction in viscosity is related to an interaction of the virus particles themselves with the viscous component of inhibitor solutions.

There are several reasons for supposing that the relationship of the EW inhibitor of hemagglutination to the viscous component of solutions of purified inhibitor is one of identity: (a) both the inhibitor and the viscous component appear capable of interacting with virus; (b) both suffer a change when treated with unheated virus, and both are less susceptible to action by heated virus; (c) the viscous component has probably a high molecular weight, and it is likely that any material of high molecular weight which is capable of combining with virus would be capable also of inhibiting virus hemagglutination; and (d) the specific viscosity of the two purified inhibitor preparations, A178 PIII EI and A180 PEI, which have been studied in detail, is proportional to the inhibitory activity. Calculated on a nitrogen basis, the activities of these preparations were 41 and 60 times, respectively, that of EW, and the specific viscosities at 30 $\gamma$ N per ml were 0.075 and 0.105. This proportionality becomes a valid test when it is considered that the viscosity of purified inhibitor solutions is contributed chiefly by a component (or components) which is susceptible to virus action, as inferred from the low terminal viscosities of virus inhibitor mixtures.

The reduction in viscosity induced by virus may be interpreted as a reduction in the asymmetry of the molecules (or particles) susceptible to virus action. There are several obvious and quite different ways by which such a change in shape could be achieved: (a) the molecules could be fragmented across the long axis; (b) they could be made to fold or coil without change in size; (c) they could be made to condense with one another with simultaneous increase in size and decrease in asymmetry; and (d) they could form suitable stable complexes with virus particles. Of these ways, the first three could be thought to depend on an enzymatic action of the virus, while the fourth could be regarded as a process of stable aggregation of inhibitor molecules and virus particles. Support for the latter explanation is provided by the observation (*6*) that a precipitate forms at interfaces between EW and purified virus preparations. No definite evidence of precipitation has been obtained, however, in the present experiments with dilute solutions of purified inhibitor; and since inhibitor virus mixtures which have been incubated for long periods possess considerable hemagglutinative activity, comparable to that of uninhibited virus, it is likely that the virus separates from the viscous component after interaction. Accordingly, an enzymatic hypothesis of virus function offers the most reasonable explanation at the present time of the virus induced reduction in viscosity of solutions of purified inhibitor. This hypothesis is compatible also with the relative independence of the terminal viscosity on initial virus concentration and with the failure of repeated additions of fresh inhibitor solution to affect appreciably the viscosity reducing capacity of virus.

If the above interpretation is correct, the present observations provide the most direct demonstration, so far as we are aware, of an enzymatic action of influenza virus on a relatively pure and simple substrate. It should be mentioned that several previous attempts (*1*, *2*) at such a direct demonstration have failed.[3]

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## A New Human Hereditary Blood Property (Cellano) Present in 99.8% of all Bloods


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A new agglutinogen of human blood was recently observed with the aid of an immune agglutinin produced by a mother of an infant with a mild form of hemolytic disease.[1] This antibody, which behaves like a "warm" agglutinin (*4*), is remarkable because of the unusually

[1] The diagnosis was made by Dr. Eric Ponder on the basis of clinical and hematologic studies.

[3] While this paper was in press, D. W. Wooley (*J. exp. Med.*, 1949, **89**, 11) reported changes in the viscosity of erythrocyte extracts on treatment with influenza virus A (PR8 strain).

high incidence of positive reactions (99.8%) in tests of 2500 blood specimens submitted for Rh testing. When first studied in May 1947, its titer at 37° C, in saline, was 1:64 and 18 months later its activity was only slightly diminished (1:32). Its titer was 1:1 at 20° C and 1:4 at 5° C. Absorption experiments with numerous blood specimens of different antigenic structure indicate that the high incidence of positive reactions is attributable to the action of a single antibody.

For want of a better name, this blood factor will be referred to by the patient's name, "Cellano", and its antibody as "anti-Cellano."

Of the 2500 blood specimens tested with anti-Cellano, more than 90% were from women whose Rh negative blood was submitted for antibody determination. Excluding the blood of the immunized mother, only five were found to lack the Cellano factor (0.2%). The antigenic structure in these five and in the patient's blood is given below:

| | | | Reactions with Anti- | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | D | C | E | c | | |
| 1. Patient Cellano | A | N | + | + | o | + | Rh pos. | ($Rh_1$) |
| 2. Mrs. B. M. | O | MN | o | o | o | + | Rh neg. | |
| 3. Mrs. B. H. | A | M | o | o | o | + | Rh neg. | |
| 4. Mrs. R. C. | A | MN | o | o | o | + | Rh neg. | |
| 5. Mrs. L. | O | MN | o | o | o | + | Rh neg. | |
| 6. Julian K. | B | M | + | + | o | + | Rh pos. | ($Rh_1$) |

The findings in the family of Julian K., whose blood lacks the factor, follow:

| | | | Reactions with Anti- | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | D | C | E | c | | | Cellano |
| Father: | | | | | | | | | |
| John K., Sr. | O | MN | + | + | + | + | Rh pos. | ($Rh_1Rh_2$) | + |
| Mother: | | | | | | | | | |
| Mary K. | AB | M | o | o | o | + | Rh neg. | | + |
| Children: | | | | | | | | | |
| 1. John | A | MN | + | o | + | + | Rh pos. | ($Rh_2$) | + |
| 2. Julian | B | M | + | + | o | + | Rh pos. | ($Rh_1$) | o |
| 3. Mrs. I. S. | A | M | + | + | o | + | Rh pos. | ($Rh_1$) | + |
| 4. Mrs. A. G. | A | M | + | + | o | + | Rh pos. | ($Rh_1$) | + |
| 5. Mrs. A. V. | A | M | + | + | o | + | Rh pos. | ($Rh_1$) | o |
| 6. Frank | B | M | + | + | o | + | Rh pos. | ($Rh_1$) | o |
| 7. Andrew | A | MN | + | + | o | + | Rh pos. | ($Rh_1$) | + |
| 8. Josephine | A | MN | + | + | o | + | Rh pos. | ($Rh_1$) | + |

Apparently, both parents are heterozygous for the factor so that 25% of the offspring are expected to be Cellano negative. Of the eight children tested, three were found to lack this new property.[2]

Assuming the presence of two genes at a particular locus on one of the chromosomes, their incidence could be calculated as follows:

Let $Y$ = gene determining the presence of the Cellano factor and $y$ = gene determining the absence of the Cellano factor

Then (1) $Y + y = 1$

(2) $y = \sqrt{\text{Cellano negative}} = \sqrt{.002} = .045 = 4.5\%$

(3) $Y = 1 - .045 = 0.955 = 95.5\%$

(4) $Y^2 + 2Yy + y^2 = 1$

(5) $(.955)^2 + 2(.955)\ (.045) + (.045)^2 = 1$

(6) Cellano homozygous = .912 or 91.2%
Cellano heterozygous = .086 or 8.6%
Cellano negative = .002 or 0.2%

Blood lacking the factor can be expected only in the offspring of the following matings:

$Yy \times Yy = 8.6 \times 8.6 = 0.74\%$ of all matings (1:135)
$2Yy \times yy = 2(8.6)(0.2) = 0.03\%$ of all matings (1:3333)
$yy \times yy = (0.2)(0.2) = 0.0004\%$ of all matings (1:250,000)

In the remaining matings (99.23%), all the offspring must be Cellano positive.

In a series of 150 Negroes, all blood specimens were found to contain the Cellano factor.

In the white population of the United States, the Cellano factor has a greater incidence than any other factor, exceeding the factor e (h″) by 2.8% (7). In this connection, it may be noted that in American Indians (3), and Chinese (6), the D factor ($Rh_o$) has an incidence of 99% or higher, and certain races of American Indians are almost exclusively of group O.

Correlated studies indicate that the Cellano factor is independent of the AB, MN, and Rh-Hr systems. This view was confirmed in a study of the Cellano serum made available to Dr. R. R. Race and his colleagues (8).

A list of Cellano negative blood is being prepared for the purpose of identification of other antibodies which are characterized by a high incidence of positive reactions. Such blood would be essential for transfusing those rare patients who may have produced this antibody and also for transfusing their affected infants.

The genetic homologue of the Cellano factor, when found, would be a blood property present in 8.8% of the same population of which 0.2% would be homozygous and 8.6% heterozygous. Two human antibodies have been described which do give a frequency of positive reactions closely approximating this value (anti-Lutheran 8% and anti-Kell 7%) (2, 1).

Parallel tests on the above-mentioned family with the anti-Cellano serum and two specimens of anti-Kell serum, one of which was supplied by Dr. R. R. Race, show that the genes for Cellano and Kell antigens are alleles (5). The findings indicate that both parents are heterozygous for Kell as well as for Cellano. This would lead to an expectation among their offspring of ¾ Kell positive and ¼ Kell negative. In exact agreement with this, and in striking contrast to the frequency of 8.8% calculated to exist in the entire population, six of the eight children were Kell positive.

For the sake of uniformity, the letters "$K$" and "$k$," already used by the British workers for the genes determining Kell positive and Kell negative reactions respectively, will be retained (9). The observations with anti-Cellano indicate that the gene $k$ can now be considered as indicating the presence of the Cellano factor. As in the case of $M$ and $N$ and the three Rh-Hr systems,

[2] For these specimens the authors are indebted to Mr. Benson Rosenberg, Elizabeth Biochemical Laboratory, Elizabeth, New Jersey, who also tested 350 random blood specimens, all of which contained the Cellano factor.

there are three genotypes (*KK*, *Kk*, *kk*) corresponding to three phenotypes.


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## A New Time Scale for Kymograph Recording


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In laboratory experiments involving the kymograph recording of biological responses a time line is generally traced on the smoked paper, together with the experimental record. This time line allows the observer to correlate the observed phenomenon with absolute time.

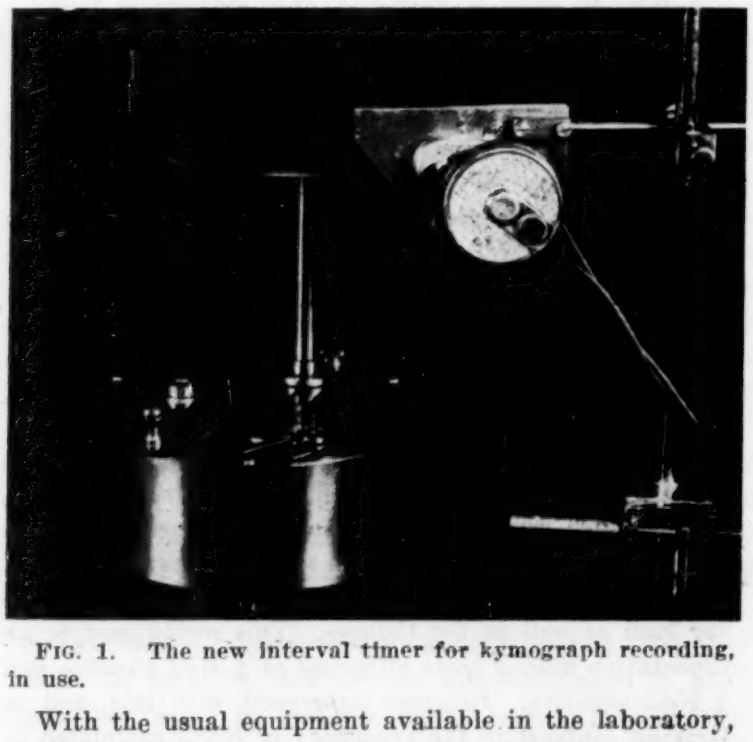

FIG. 1. The new interval timer for kymograph recording, in use.

With the usual equipment available in the laboratory, tracing this time line involves the use of signal magnets, dry cells, and a signal source. Failure on the part of any of these units leads to inconveniences. When the signal source is centrally located and is used by several investigators in different experiments, the adjustment of the signal may not be suitable for all. To overcome these troubles, a small instrument which is independent of such auxiliary apparatus has recently been developed. This instrument is a small self-contained unit (Fig. 1) which will trace a characteristic time scale when plugged into any 110-volt, 60-cycle circuit. Although the intervals on this scale are not adjustable, the form of the time scale traced makes it suitable for use over a wide range of kymograph speeds. (See Fig. 2.)

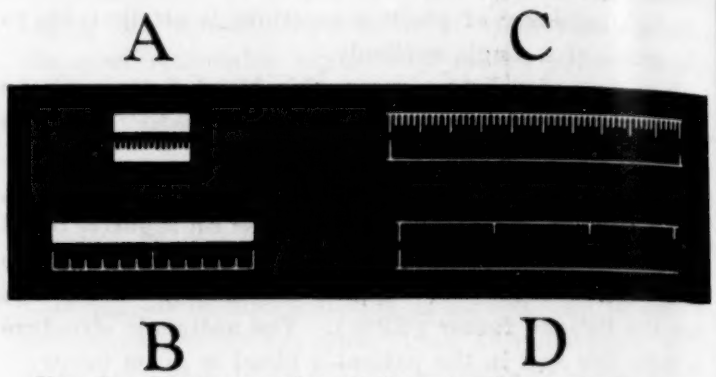


FIG. 2. Four examples of the new time scale for kymograph recording, illustrating its enormous range. The upper base line indicates intervals of 1 sec (long lines) and ⅕ sec (short lines). The lower base line similarly indicates 1-min and 10-sec intervals. Note that, at very slow drum speeds, the 1-sec and ⅕-sec divisions merge into a solid phalanx. (A) At drum speed of 0.5 mm/min. (B) At drum speed of 10 mm/min. (C) At drum speed of 200 mm/min. (D) At drum speed of 3000 mm/min.

The instrument used to trace the time scale operates as follows: Two very light styli (A and B in Fig. 3) spaced 4 mm apart trace the base lines. The upper stylus (A) is struck from above by an impactor (C) at a rate of five impacts per sec. Every fifth impact is heavier than the others. This results in the tracing of a longer line than the others. Thus 1-sec division lines are traced, each divided by four shorter lines representing 1/5-sec intervals. These lines extend downward from the upper base line. The lower stylus (B) is struck from below by another impactor (D) at a rate of one impact in 10 sec, each sixth impact being heavier than the others. Thus 1-min division lines are traced, each minute being divided into six divisions of 10 sec each. These lines extend upward from the lower base line. The adjustment is such that the 1-min and 10-sec divisions align exactly with the corresponding 1-sec division lines. The impactors are operated by cams (E and F) driven by a small self-starting synchronous motor. The accuracy of

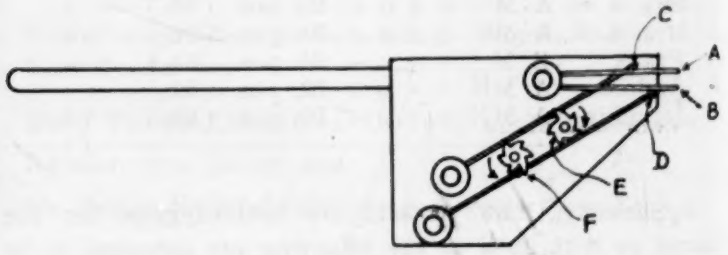


FIG. 3. The new interval timer for kymograph recording, as seen from the rear with cover removed.

[1] I am grateful to Dr. Warren H. Yudkin (now at Cambridge University, England) for pointing out the inconveniences of older methods and for requesting a solution of the problem, and to Dr. Edgar J. Boell of Yale University for making available to me facilities for testing the timer and for his helpful advice.

the intervals is ensured by the 60-cycle alternating current.

Both impactors follow a path of motion which is oblique to the deflection of the styli levers. The object achieved by this disposition of the impactors is the dissipation of sufficient energy by frictional contact to prevent rebound, which would cause the tracing of fuzzy division lines between intervals. The impactors are light in weight and do not strike the styli until they have reached their maximum velocity. Their high velocity is then transmitted to the styli, ensuring sharp graduations.

Records made with this instrument are shown in Fig. 2. It is apparent that, at either moderately slow or moderately fast speeds of the kymograph drum, the time scale traced on the paper can be read clearly. Due to the nature of this time scale no adjustment of the intervals traced by this instrument is necessary when changing drum speeds within very wide limits.

A new nonadjustable interval timer is described which traces a characteristic time scale on kymograph records (Fig. 2). The distinctive nature of the time scale traced allows its use on most records of moderate speed. It records intervals from 1/5 sec to 1 min. The timer described is a self-contained unit which requires no dry cells or signal magnet but merely an electricity supply of 110-volt, 60-cycle alternating current.

## Induction of Cytogenetic Changes and Atypical Growth by Hexachlorocyclohexane

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We have treated with insecticides containing hexachlorocyclohexane the seedlings of the following plants: *Zea mays, Triticum vulgare, T. monococcum, T. compactum, Secale cereale, Setaria italica, Panicum miliaceum, Helianthus annuus, Crepis capillaris, Vicia faba, V. sativa, Brassica nigra,* etc. The insecticides chiefly used were: Agrocide 7, Agrocide 3, hexachlorane, 666. The main active substance of the first two is the gamma isomer of 1,2,3,4,5,6-hexachlorocyclohexane. The others contain gamma isomer and some of the other isomers. Crystals of almost pure gamma isomer display the same activity as these.

The cytological studies of the affected root, stem, and coleoptile tissues show that the agents act first upon the cytoplasm and interfere with the cytoplasmic processes involved in the formation of achromatic figures. The chromosomes do not arrange in an equatorial (metaphase) plate after prophase, but remain scattered approximately as they are during the prophase. They appear less bent than usual. The thickening of the chromosomes and their reproduction and splitting proceed, regardless of the fact that the processes involved in the formation of achromatic figures are highly disturbed or even entirely inhibited. Poles are not formed. After reproduction, the chromatolytic (nucleoproteolytic) processes proceed, and a nucleus is formed containing twice as many chromosomes as at the start of the abnormal mitotic processes. The main trend of the processes of chromosome doubling recalls those induced by colchicine, acenaphthene, and other polyploidizing agents.

Since the insecticide continues to act further, the next abnormal (Ab-) mitosis ends with a second chromosome doubling, and so on. Thus tetraploid and octoploid cells and cells of a much higher polyploid degree are formed. Along with these, certain diploid cells that have not yet undergone Ab-mitosis can still be found.

Chromosome multiplication leads to increase in the size and occasionally in the number of the nuclei and further to increase in the size of the cells. Thus the cells grow instead of multiplying and differentiating, bringing about the swelling of the roots, stems, and coleoptiles.

The chromosome reproduction and separation in *Zea mays* should be considered as a somewhat special case. We have observed in a series of cells that the chromatids of the somatic chromosomes bend at the centromeres reciprocally toward each other, each being shaped like a V, and together forming a X, the chromatids being attached at the centromere. These figures can be interpreted by postulating certain repulsion forces existing between the chromatids, the reproduction (or division) of the centromere being somewhat delayed. This phenomenon occurs when the chromatic figure is highly or completely disturbed. In other words, it does not seem to be regulated to a very great extent by the forces exerted by the achromatic figure.

The solubility of hexachlorocyclohexane in water is very low; therefore, it is applied in the form of small solid particles. The particles act when they are in contact with the plant tissue. It has a specific odor, but the experiments failed when we tried to induce specific atypical growth from a distance. In this respect its effect differed from that of acenaphthene. For the sublimating particles of the acenaphthene act even when the crystals are not in contact with the plant tissue.

The effect of hexachlorocyclohexane is so striking that it can be used as a polyploidizing agent, especially when one considers that it is much cheaper than other such agents.

In certain cases one or more chromosome groups may move slightly in various directions into the cytoplasm. Such a slight separation may occasionally end in the formation of two or more aneuploid nuclei; thus polynucleate cells or cells with monstrously deformed nuclei arise. In certain cases a cell wall is formed between such nuclei. This leads to the formation of cells with aneuploid chromosome numbers. Dead cells were occasionally found in the roots, stems, and coleoptiles; they may have been aneuploid.

All these phenomena are due to the activity of the agent upon the cytoplasm.

The active agent may also induce certain changes in the nuclear elements, i.e., in the chromosomes. Chroma-

tid and chromosome fragments were also observed, although rarely.

Such insecticides or fungicides, when applied, may increase hereditary changes in cultivated varieties (''pure lines''), leading thus to more rapid degeneration of the highly bred, uniform varieties. This means that when such insecticides or fungicides are applied the seeds of the propagated varieties should be changed more often so as to secure new nondegenerated stocks.

## Rumen Bacteria in Cobalt-Deficient Sheep

**Lorraine S. Gall,[1] S. E. Smith, D. E. Becker, C. N. Stark, and J. K. Loosli**

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In 1944, McCance and Widdowson (*4*) suggested that cobalt may function in connection with the rumen bacteria. This view was based on a communication from C. J. Martin who stated that sheep suffering from ''Coast Disease'' were cured by feeding cobalt but not by cobalt injection. Cobalt deficiency does not occur in horses, according to Marston (*3*). Attempts to produce cobalt deficiency in rats (*3, 8*) and in rabbits (*7*) have been unsuccessful. Thompson and Ellis believe that cobalt is needed only by ruminants and that it may be concerned with biological processes in the rumen. Recently, Ray *et al.* (*5*) observed a definite response in hemoglobin and gain in weight in cobalt-deficient sheep injected with cobalt, but the response was much less than in animals fed cobalt.

In an attempt to obtain direct evidence which might show with some certainty whether or not cobalt deficiency influenced the bacteria of the rumen, studies were undertaken to measure the bacterial activity of rumen samples. Twenty-one Western yearling sheep became cobalt-deficient after being fed a ration low in cobalt for 8 months. At this time the sheep were losing weight, and had poor appetites and low hemoglobin values (*6*). These sheep were then divided into three equal groups. The first group was fed 1 mg of cobalt per day, while the second received the same amount of cobalt by injection. The remaining seven sheep were kept on the deficient ration. After 1 week sheep fed cobalt were gaining weight, and had good appetites and increased hemoglobin values, while those on the basal ration alone or those injected with cobalt continued to decline. At this time the rumen contents of four sheep from each group were sampled by stomach tube for bacteriological study, and the remaining sheep were sampled the following week. Six additional sheep were maintained for 1 month on a restricted feed intake comparable to that of the cobalt-deficient sheep. These sheep were then sampled to determine the effect of lowered feed intake *per se* on rumen bacteria. The sheep received adequate cobalt in the ration and a 60% or more of the ration eaten by the sheep fed cobal The kinds and number of bacteria present in the rume contents of the four groups of sheep were compared b means of Gram stains, direct slide counts, and anaerob cultures (*1*).

The results of the slide counts and cultural tests a summarized in Table 1.

TABLE 1

INFLUENCE OF DIET ON RUMEN BACTERIA

| Dietary group | No. of animals | Bacterial slide count | Cultural results—No. growing in dilutions $10^{-7}$ | $10^{-8}$ | $10^{-9}$ | $10^{-10}$ | $10^{-1}$ |
|---|---|---|---|---|---|---|---|
| | | *billions/gm* | | | | | |
| Cobalt-deficient | 7 | 30.2 | 7 | 7 | 2 | 0 | 0 |
| Cobalt injected | 7 | 30.7 | 7 | 5 | 3 | 0 | 0 |
| Cobalt fed | 7 | 54.6 | 7 | 7 | 7 | 5 | 2 |
| Restricted feed intake | 6 | 56.3 | 6 | 6 | 5 | 3 | 1 |

Culturally, there were major differences between the dietary groups. The samples from sheep fed cobal gave the highest cultural counts, all cases showing growth in the $10^{-9}$ dilution, 5 in $10^{-10}$, and 2 in $10^{-1}$ dilution of rumen contents. In marked contrast, only 2 cobalt-deficient and 3 cobalt-injected animals showed bacterial growth in the $10^{-9}$ dilution, and neither group gave growth above this dilution. Bacteriologically, sheep on restricted feed intake but fed sufficient cobalt resembled those fed cobalt and unlimited feed. Both the kinds and numbers of bacteria in the rumen content of sheep fed cobalt resembled those of sheep fed normal rations (*1*).

It can be seen by slide count that cobalt-fed sheep had almost twice as many bacteria per g of rumen contents as cobalt-deficient and cobalt-injected animals. The bacterial slide count of sheep on restricted feed intake was about the same as that of sheep fed cobalt.

Gram stains of samples were identified only by number, which had no significance to the examiner, but after microscopic study it was possible, on the basis of the stains alone, to separate cobalt-deficient sheep from cobalt-fed animals. In 5 out of 7 cases, Gram stains from cobalt-injected sheep were grouped with cobalt-deficient sheep; while in the other two instances, the bacterial picture was not clearly typical of either group.

Gram stains from sheep fed cobalt were characterized by the usual wide variety of bacteria with large numbers of *Gram-positive, slender curved rods,* and *coccoid types* of bacteria covering the fibers, which were in an advanced stage of decomposition. The slides from cobalt-deficient and cobalt-injected sheep were recognized because of a complete lack of slender curved rods, and a great reduction in the numbers of coccoid forms on the fibers. The fibers were only slightly disintegrated. The differences in the bacterial picture between the groups lay more in the absence of these bacteria in cobalt-deficient and cobalt-injected animals than in a complete change of flora. Gram stains from sheep on

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restricted feed intake were similar to those of animals fed cobalt.

These data show that in cobalt deficiency marked alterations occur in the types and numbers of bacteria in ruminants and that these bacteriological changes are not caused by lowered feed intake of the deficient animals.

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## Spectrophotometric Determination of Amino Acids by the Ninhydrin Reaction


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In view of the growing interest in the separation of amino acids by partition paper chromatography (*1*, *2*, *3*, *4*, *7*, *8*), studies have been made to determine if a quantitative relationship might be established in the colorimetric reaction between ninhydrin and the amino acids. Harding and MacLean (*5*) first developed this reaction and later (*6*) condemned it as a colorimetric method for amino acid determination. In mixtures of amino acids they found a lack of specificity and a variation in the red and blue colors produced in the reaction, since ammonia and amines other than amino acids formed similar colors with ninhydrin.

Solutions of 13 amino acids were prepared by dissolving 2 mg of each in 80% ethanol. The ninhydrin reagent was prepared by dissolving 200 mg of ninhydrin in 100 ml of isobutanol. Fifty γ of each amino acid were placed into a test tube, 2 ml of ninhydrin reagent added, and the total volume made up to 10 ml with isobutanol. It was observed in many trials that the color would develop by itself at room temperature. However, to make conditions uniform, all tubes were incubated at 80° C for 3 min, removed, and cooled under running water to 22° C for 3 min. Each tube was then immediately placed in a Coleman No. 6 spectrophotometer, and the transmission determined at 10 mμ intervals between 400 and 700 mμ against a standard containing 2 ml of ninhydrin reagent and 8 ml of isobutanol until the inflection point was approached when the measurements were made at 5 mμ intervals.

The wavelengths corresponding to the inflection points in the wavelength-% transmission curves of amino acids are presented in Table 1.

TABLE 1

Wavelength of Maximum Absorption of Amino Acids Reacted with Ninhydrin

| Amino acid | Wavelength in mμ | Amino acid | Wavelength in mμ |
|---|---|---|---|
| Phenylalanine | 530 | Glycine | 555 |
| Lysine | 545 | Methionine | 560 |
| Threonine | 550 | Valine | 560 |
| Tryptophane | 550 | Arginine | 560 |
| Alanine | 550 | Norvaline | 560 |
| Asparagine | 550 | Isoleucine | 565 |
| Leucine | 555 | | |

Serial dilutions of the amino acids were made and, after reaction with ninhydrin, measured spectrophotometrically at the appropriate wavelength. The quantitative limits in γ, within which it appears possible to measure spectrophotometrically amino acids which have reacted with ninhydrin under the described conditions, that is, the limits at which the points of a plot of concentration vs. logarithm of transmission fall on a straight line, are presented in Table 2.

TABLE 2

Limits of the Spectrophotometric Determination of Amino Acids Reacted with Ninhydrin*

| Amino acid | Concentration (γ per 100 ml) | Amino acid | Concentration (γ per 100 ml) |
|---|---|---|---|
| Phenylalanine | 10–140 | Threonine | 20–130 |
| Isoleucine | 20–125 | Tryptophane | 20–200 |
| Leucine | 10–100 | Glycine | 10– 80 |
| Lysine | 5– 50 | Alanine | 10– 80 |
| Methionine | 10–100 | Asparagine | 20–180 |
| Valine | 10–100 | Norvaline | 10– 70 |
| Arginine | 20–100 | | |

* Within these limits the transmission was a straight line.

From the results of these determinations it appears feasible to adapt these studies to the quantitative estimation of amino acids separated by the partition paper chromatographic method. Transmission curves could be determined, and the quantities of specific amino acid present thereby measured in appropriate dilution.

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# *Book Reviews*

***The conquest and colonization of Yucatan, 1517–1550.*** (Publ. 582.) Robert S. Chamberlain. Washington, D. C.: Carnegie Institution, 1948. Pp. vii + 365. (Illustrated.) $4.75, paper; $5.50, cloth.

In any historical or scientific writing, the background of the author plays an important part. Probably few historians in the American field have a more imposing background in the history of Spanish conquests than Robert Chamberlain. The number of bibliographical works concerning Spanish conquests in Yucatan, especially by those conquistadores, the Montejos, have largely resulted from Robert Chamberlain's researches. This book may be regarded as the consolidation of a whole series of accomplishments in this direction.

The author has pointed out the great importance of an exhaustive work concerning the conquest of Yucatan. This phase of the New World enterprises of the Spanish is certainly the least known of any. The conquest of the Valley of Mexico and of the surrounding peoples has been exhaustively chronicled from several viewpoints. Spanish entradas in northern Mexico and the Southwest have also aroused considerable historical enthusiasm. Pizarro's conquests of the vast Inca state are known to every casual student. The more important explorations and conquests of Yucatan by the Spanish have been heretofore inexplicably slighted. Yucatan was the first portion of the mainland of the Americas west of Cuba to be discovered, but it was the last area of these coasts to be subjugated. This sequence seems to have been followed by present day scholars. Even the name of the great conquistador, the Adelantado, Francisco de Montejo, is little known. Robert Chamberlain ably brings out the qualities of Montejo during the many difficulties of the Spaniards in exploring and pacifying Yucatan. The publication of *The conquest and colonization of Yucatan* assures the name of Montejo its just place with Cortés, Pizarro, Balboa, Jiménez de Quesada, Alvarado, and Valdivia.

The Spanish history in relation to Yucatan is closely followed from the time of the discovery and the initial phases of the conquests, through the many entradas and colonization attempts, to the final conquest after the great Maya revolt. The last portion of the book deals with the first years of the colony to the middle of the 16th century. Francisco de Montejo, into whose hands the Castilian Crown gave the occupation of Yucatan, had interests in addition to Yucatan proper; consequently the history includes other areas adjacent to Yucatan. Montejo had his eyes fixed on other areas—Honduras and Higueras, the region of Golfo Dulce and Chiapas. The history of these neighboring provinces was inextricably interwoven with that of the Mayan area.

It would be a strange book indeed that a reviewer could not criticize in some minutia. The controversial points are of little importance, however. In cases of possible doubt the author has carefully cited the original texts in elaborate footnotes. By the very nature of these early sources, there were controversial accounts and mutually exclusive data and dates. The author has reviewed and weighed the evidence carefully in all cases. In many instances Mr. Chamberlain has exhibited a thorough knowledge of the background of his subject over and above purely historical facts. He displays an intimate acquaintance with the encomienda system, for example, without which knowledge much of the Spanish history in Yucatan is inexplicable. The bibliography and footnote structure of this book convinces this reviewer that the author has made adequate use of all known sources relating to the history and conquest of Yucatan.

*The conquest and colonization of Yucatan* is a significant work on the background of the European advent in the Americas. Between two covers, Robert Chamberlain has collected all of the data pertinent to this period, indicated the significant features, and authenticated the whole.

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***Fatigue and impairment in man.*** S. Howard Bartley and Eloise Chute. New York: McGraw-Hill, 1947. Pp. 429. $5.50.

This book proposes a thesis that conflict and frustration are cardinal factors in the etiology of fatigue and at the same time provides, unwittingly, excellent material for testing this hypothesis. For the reviewer, the theory has "worked." He became frustrated. And he became tired. On checking with others who read the volume he was able to verify that his was not an exceptional, idiosyncratic reaction.

Throughout, the treatment suffers from a basic dilemma. Arbitrarily, the authors limit the meaning of fatigue to the experience of feeling tired. They use the term impairment for the objective, biochemical and physiological alterations present in a variety of situations in which the human organism is placed under strain. Their primary interest is in fatigue, not in impairment. Yet most of the book is devoted to impairment. The result is a definite lack of balance.

There is need for a detailed summary of the results and problems of "stress" physiology, taking into account the phenomena of both adaptation and breakdown of the adaptive mechanisms. This need became even more acute as a result of the accumulation during the war years of a large mass of new data on the effects of

extremes of environmental temperature, high altitude, nutritional deficiencies, strenuous work, participation in combat, etc. This undertaking is beyond one man's competence and capacity. At any rate, the summary attempted by Bartley and Chute does not fill the need for a comprehensive and up-to-date treatment.

The part devoted to fatigue as a subjective experience is also unsatisfactory, but for other reasons. The amount of valid and usable information available in the literature is small and there is, consequently, little to summarize. Bartley's own work in this area is very limited. The role of "conflict" in the causation of fatigue was developed in the course of his studies on the pupillary reflex (1942). Later (1943) conflict (and frustration), defined as "any clash, incompatibility or disharmony occurring at any level of organismic activity," was assigned a universal role in fatigue. Most of the discussion is based on arm-chair analysis.

The emphasis on the attitudes and motivation of persons in whom fatigue is being studied is wholesome. Few will disagree with the author's statement that the subjective phenomena of fatigue cannot be treated in a simple quantitative fashion. However, no constructive suggestions, useful to the experimenter or the clinician, such as using more sophisticated, standardized inventories, were submitted. Improved methods are a *sine qua non* condition of rising above the stage in which "most of what we know about fatigue arises from everyday observations and from deductions made from these" (p. 400).

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*University of Minnesota*

***Scientific and industrial glass blowing and laboratory techniques.*** W. E. Barr and Victor J. Anhorn. Pittsburgh, Pa.: Instruments Publ., 1949. Pp. viii + 380. (Illustrated.) $6.00.

Three objectives are outlined and admirably attained in the 15 chapters of this book. The first objective is to give instruction in glass blowing, with many elementary details and drawings, covering a simple junction of two pieces of glass and ending with the making of a complicated ground glass stopcock. Shop layout, burner designs, the chemical and physical properties of glasses of American and imported types and other related topics help to broaden the reader's knowledge. A chapter on glass-to-metal seals covers the principles involved, the combinations of metals and glasses available, their properties, and the production of lamps and tubes with such seals.

The second objective is to present advanced techniques required for the production of high vacua. Two chapters describe many types of vacuum pumps and vacuum gages in great detail, including their calibration and uses. There is a chapter on high vacuum techniques which includes silvering methods, gas evolution from hot glass, and a host of other items.

The third objective is to describe in great detail four types of special glass equipment with the aid of other authorities, such as Joyner on gas adsorption apparatus, Hanson on molecular weight apparatus, Anderson on Swietoslawski ebulliometers. A long chapter is devoted to distillation problems, including theoretical discussion and operating requirements of fractionating and distillation columns and condensers. Vacuum fractionating equipment and molecular stills also are described.

Each chapter is concluded with adequate literature references, and the index refers to subject matter only. The book will appeal to people of varying interests, but the emphasis is mainly on chemical scientific apparatus and the title might well have indicated this. There will be differences of opinion on the details of construction, but not on the main points covered. With so much material there are bound to be errors, such as the Dushman reference on page 191, and the chemical composition of DG glass on page 124.

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***The essentials of organic chemistry.*** C. W. Porter and T. D. Stewart. Boston, Mass. and London, Engl.: Ginn, 1948. Pp. vi + 394. (Illustrated.) $4.00.

Professors Porter and Stewart have provided a textbook for a short course in organic chemistry. They have covered most of the basic and established facts and theories of this branch of learning in a simple style that should be easily comprehensible to a beginning student. The book is designed primarily for nonscience majors. It is equipped with exercises and problems at the end of each chapter and with adequate diagrams, tables, and equations to illustrate the textual discussions.

It should have been possible for the authors to incorporate some of the more important and interesting new products, processes and theories without lengthening the book unduly. Such developments as the silicones, the oxo process, and the carbonium ion theory of rearrangements are either not mentioned or are inadequately treated. Statements such as the following are inaccurate or grossly misleading: "Animal parasites are called trypanosomes; examples are the hookworm, the amoeba which causes dysentery, . . ." (p. 361); "A reaction which is not given by aliphatic ketones, but which occurs readily with aromatic ketones, is the Clemmensen reduction" (p. 331); "The hydroxyl group of a phenol, however, may be replaced with chlorine by heating the phenol with phosphorus pentachloride" (p. 300). The last statement is not qualified in any way and creates the false impression that satisfactory yields are ordinarily obtained with all phenols.

Aside from this sort of inaccurate statement, however, the book is remarkably free from errors. It is well printed and bound and presents an attractive appearance. The authors have produced a work which should be popular in many colleges.

G. B. BACHMAN

*Purdue University*

# Association Affairs

**Local Committees for the 1949 Annual Meeting of the AAAS in New York City.** The establishment of local committees to direct the preparations for the 116th Meeting of the American Association for the Advancement of Science, December 26–31, in New York City, began auspiciously when **J. W. Barker,** president of Research Corporation and formerly dean of the Faculty of Engineering, Columbia University, accepted appointment as general chairman, with the responsibility of coordinating the activities of all local committees. Dr. Barker, whose training was received in the University of Chicago and Massachusetts Institute of Technology, is eminently qualified for this post. In World War I he rose from second lieutenant to major in the Coast Artillery Corps and served on the faculties of M.I.T. and Lehigh before assuming the deanship at Columbia. Dr. Barker has been vice president of the American Institute of Electrical Engineers and vice president and president of the Illuminating Engineering Society; he was special assistant to the Assistant Secretary of the Navy, and in 1937 he was chairman of AAAS Section M.

A local Advisory Committee, headed by **George B. Pegram,** vice president of Columbia University (the general chairman of the 1928 New York City Meeting) and including **William J. Robbins,** director of the New York Botanical Garden; **Albert E. Parr,** director of the American Museum of Natural History; and **Sam F. Trelease,** Torrey Professor of Botany, Columbia (on the General Local Committee in 1928), has been serving since early March. The complete personnel of the local committees on Reception and Entertainment, Equipment and Projection, Publicity, Finance, Reference, and General Sessions and Lectures will be announced in *Science* when they are organized. The success of the Annual Meeting of the Association depends in very large measure on the efforts of the local committee members who give so generously of their time; this will be particularly true of the New York City Meeting.

In order to increase participation in the **Gordon Research Conferences** (to be held this year at Colby Junior College, New London, New Hampshire, from June 20 to September 2, as announced in *Science,* March 4), two significant procedures have been established by recent action of the Management Committee and the Advisory Board. First, the registration fee has been increased to provide each conference with a small fund to pay part of the expenses of participants who would otherwise be unable to attend, the money to be allocated by the chairman in consultation with the director. And second, the advisory board has been enlarged to include fifteen nonsponsor representatives from colleges and universities. Five individuals are to be elected each year for a term of three years. The first five elected this year are Paul Bartlett, Harvard University; John Bowman, Mellon Institute of Industrial Research; C. A. Elvehjem, University of Wisconsin; Paul Flory, Cornell University; and H. S. Taylor, Princeton University.

The Management Committee, in cooperation with the Advisory Board, is responsible for operating the annual conferences. The Advisory Board consists of an official representative from each of the 57 industrial companies that sponsor the conferences through the American Association for the Advancement of Science. Members are named by the sponsors and serve indefinitely. The conference chairmen each year also serve on the Board. The Management Committee is elected from the Advisory Board, two members being chosen each year to serve for a term of three years. The present committee is Emil Ott, chairman, Hercules Powder Company; K. G. Compton, vice chairman, Bell Telephone Laboratories; Dean Burk, National Institutes of Health; George Calingaert, Ethyl Corporation; S. S. Kurtz, Jr., Sun Oil Company; Randolph T. Major, Merck & Company; Howard A. Meyerhoff, AAAS; and W. George Parks, director, Rhode Island State College.

The Management Committee selects the conference director, decides where the conferences are to be held, and concerns itself with finances and other details of operation, as well as formulating future plans and policies, for consideration by the Advisory Board. A survey of the present conferences is in progress now under the direction of S. S. Kurtz, Jr., to be used as a basis for future plans and developments.

W. George Parks.

**The Laurentian Hormone Conference** of the AAAS will hold its 1949 meeting at the Forest Hills Hotel, Franconia, New Hampshire, September 12 to 17. The following program has been arranged:

I. Ovarian Physiology and Function

*Monday evening, September 12.* Biology of the Ovary: A. S. Parkes, National Institute for Medical Research, London.

*Tuesday morning, September 13.* Physiology of Estrogenic Hormones: K. E. Paschkis and A. Rakoff, Jefferson Medical College.

*Tuesday morning, September 13.* Maintenance of the Corpus Luteum and Physiologic Actions of Progesterone: James T. Bradbury, Willis E. Brown, and Laman A. Gray, State University of Iowa and University of Louisville.

*Tuesday evening, September 13.* The Vasculature of the Ovary and Ovarian Function: S. R. M. Reynolds, Carnegie Institute of Washington.

II. Chemistry and Physiology of the Sex Hormones

*Wednesday morning, September 14.* Studies with Estrogen Conjugates: G. A. Grant and D. Beale, Ayerst, McKenna & Harrison, Ltd.

*Wednesday morning, September 14.* Chemical Methods for the Estimation of Steroid Hormones and their Metabolites: Lewis Engel, Massachusetts General Hospital.

III. Pituitary Physiology and Function

*Thursday morning, September 15.* Pituitary Control of Steroid Secretions: Roy O. Greep, Harvard School of Dental Medicine.

*Thursday morning, September 15.* The Present Status of Posterior Lobe Hormones: Robert L. Noble, University of Western Ontario.

IV. Humoral Mediators in Nervous Transmission

*Thursday evening, September 15.* Sympathetic Neurohumors: M. L. Tainter and F. P. Luduena, Sterling Winthrop Research Institute.

*Friday morning, September 16.* The Acetylcholine System in Neural Function: Ralph W. Gerard, University of Chicago.

V. Hormones and Tumors

*Friday morning, September 16.* Experimental Endocrine Tumors: George W. Woolley, Roscoe B. Jackson Memorial Laboratory.

*Friday evening, September 16.* The Virilizing Syndrome in Man: Lopis J. Soffer, J. Lester Gabrilove, Joseph W. Jailer, and Mildred D. Jacobs, Mount Sinai Hospital.

VI. Mechanisms of Hormone Action

*Saturday morning, September 17.* Effects of Hyperglycemic Factors of the Pancreas and of Epinephrine on Glycogenolysis: Earl Sutherland, Washington University, St. Louis.

*Saturday morning, September 17.* Hormone-Enzyme Relationships: Roland K. Meyer, University of Wisconsin.

Attendance is limited by the available hotel accommodations, but the Committee on Arrangements invites applications for attendance from interested investigators and specialists in the hormone field. The Committee consists of R. W. Bates, E. R. Squibb & Company; E. C. Reifenstein, Jr., Sloan-Kettering Institute; A. White, School of Medicine, University of California at Los Angeles; and G. Pincus, Chairman, The Worcester Foundation for Experimental Biology. Applications for attendance should be sent to the Chairman at 222 Maple Avenue, Shrewsbury, Massachusetts, and must be received by *June 6.*

**The Springfield chapter of the AAAS** met March 31 at American International College. Dr. S. A. Simon, Chicopee Manufacturing Company chemist, spoke on the subject of fibers, discussing their synthesis, structure, function, and purposes, in nature and in the laboratory, and the techniques used to study them.

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# *NEWS and Notes*

**Charles E. Sando,** U. S. Department of Agriculture plant chemist, has been named project advisor for USDA Research on Crop Utilization, Bureau of Agricultural and Industrial Chemistry. Dr. Sando succeeds Cornelius E. Senseman, recently retired.

**Robert A. Kehoe,** of the University of Cincinnati, has received the Knudsen Award of the American Chemical Association of Industrial Physicians and Surgeons for his work in the field of industrial medicine. The award was made at the Association's annual convention held in Detroit, April 7.

Robert **Lindley Murray,** executive vice president of the Hooker Electrochemical Company, Niagara Falls, New York, has been awarded the 1949 Jacob F. Schoellkopf Medal of the Western New York Section of the American Chemical Society. Dr. Murray was cited for his engineering ability and his able direction of chemical research and development in the chlorine and alkali industry.

**Gregor Wentzel,** University of Chicago physicist, will be a visiting professor at Stanford University during the summer quarter. While there he will offer a course on recent developments in quantum electrodynamics.

The National Academy of Sciences made the following awards at its annual dinner held April 26 in Washington, D. C.: The Cyrus B. Comstock Prize of $3,500 to **Merle A. Tuve,** director, Department of Terrestrial Magnetism, Carnegie Institution of Washington, D. C., for his work in nuclear physics, geophysics, and development of the proximity fuse; the James Craig Watson gold medal and honorarium to **Samuel Alfred Mitchell,** director of the Leander McCormick Observatory, University of Virginia, for his many services to astronomy; the Mary Clark Thompson gold medal and honorarium, in absentia, to **Frank McLearn,** of the Canadian Geological Survey, in recognition of his contribution to geologic science; and the Public Welfare Medal to **George Harrison Shull,** professor emeritus of botany and genetics, Princeton University, in recognition of his improvement of the maize crop.

**Ernst Mayr,** curator of the Whitney-Rothschild Collections of the American Museum of Natural History, is serving as guest lecturer in the Department of Zoology at the University of Minnesota for the spring quarter and is offering a graduate course on the "Origin of Species and Other Problems of Evolution."

**Arvid Lundquist,** president of the American Society of Swedish Engineers in New York, has been awarded the Swedish Royal Order of Vasa, with the rank of knight.

**William T. Salter,** chairman, Department of Pharmacology, Yale University School of Medicine, was awarded the first $1,000 Iodine Educational Bureau award (see *Science*, September 17, p. 298) at the recent annual meeting of the American Pharmaceutical Association.

**Robert W. Kleemeier,** professor of psychology at Northwestern University, has been appointed director of the newly established laboratory for gerontology and geriatrics at Moosehaven, Florida, effective September 15.

**Frans Verdoorn,** botanist, has resigned as director of the Los Angeles State and County Arboretum at Arcadia, California, and will resume his editorial work at Waltham, Massachusetts. He will continue to serve the arboretum as a councilor.

## Fellowships

**The U. S. Atomic Energy Commission** has instituted fellowships to be granted to qualified investigators who wish to work with radioactive isotopes at the Marine Biological Laboratory this summer. Each fellow will receive $250, and round trip traveling expenses from his university. Laboratory fees will be paid by the Commission. The work with isotopes will be under the general supervision of G. Failla, of the Department of Radiology, Columbia University. Applications should be addressed to Dr. Charles Packard, Marine Biological Laboratory, Woods Hole, Massachusetts.

**The Allied Chemical and Dye Corporation** announces renewal of its 31 graduate fellowship offerings for 1949–50, mainly in the fields of chemistry and chemical engineering. Each fellowship provides $1,200 and tuition. Recipients of the awards and the research to be conducted are to be selected by the 24 schools to which the fellowships have been offered: University of California, California Institute of Technology, Carnegie Institute of Technology, University of Chicago, Columbia University, Cornell University, Duke University, Harvard University, University of Illinois, University of Iowa, McGill University, Massachusetts Institute of Technology, University of Michigan, University of Minnesota, Northwestern University, Ohio State University, Pennsylvania State College, University of Pennsylvania, Polytechnic Institute of Brooklyn, Princeton University, Purdue University, Syracuse University, University of Wisconsin, and Yale University.

## Colleges and Universities

**Tulane University School of Medicine** has announced the appointment of six faculty members to the staff of its newly reorganized department of psychiatry and neurology. They are: Robert G. Heath, chairman and professor of psychiatry and neurology; Robert Hodes, professor of experimental neurology; Norman H. Rucker and Theodore Treuting, assistant professors of psychiatry; Frank Garcia, instructor in neurology and neurosurgery; and David Freedman, assistant in neurology.

The United States Geological Survey will soon establish a new coal geology laboratory at **Ohio State University,** to be ready by this summer. The new laboratory is intended to bring together field and laboratory phases of coal investigations, and to facilitate the study of fossil plants that compose coal.

**The University of California** has announced that funds have been appropriated for a low-temperature laboratory at Davis to cost $1,000,000.

## Summer Programs

**The Massachusetts Institute of Technology** announces a summer program in Food Technology, June 13–July 1, under the direction of William L. Campbell, head of the Department of Food Technology; Cecil G. Dunn, associate professor of Industrial Microbiology; Ernest E. Lockhart, assistant professor of Food Chemistry; Robert S. Harris, professor of Biochemistry of Nutrition; and Bernard E. Proctor, director, Samuel Cate Prescott Laboratories of Food Technology. Inquiries regarding registration should be sent to Prof. B. E. Proctor, Room 20-C-130, M. I. T., Cambridge, Massachusetts.

**Ohio State University's Stone Laboratory** at Put-in-Bay, Ohio, will offer eight courses during the first six-week term which opens June 21. Scheduled courses include both undergraduate and advanced studies in fish ecology, higher aquatic plants, invertebrate zoology, aquatic entomology, limnology, algalogy, ornithology, and fish physiology. Special problems and research will be undertaken during the second six-week term beginning July 28. Interested students should communicate with the laboratory regarding enrollment.

**The Northeastern Section of the Botanical Society of America** will hold its third annual summer excursion in Michigan August 20–28, under the auspices of the Cranbrook Institute of Science and the Botany Department of the University of Michigan. Registration by members will be accepted by Elzada U. Clover, Department of Botany, University of Michigan, Ann Arbor, until July 15. Nonmember registrations will be accepted if space is available. Further information may be obtained from Prof. Clover.

## Meetings and Elections

The American University announces a five-day **Institute on Scientific Research and Development,** to be held June 5–10 in Washington, D. C., with the cooperation of the National Research Council and the AAAS. Persons engaged in administration of scientific research and development activities are eligible to attend the Institute.

Five major areas will be explored during several sessions of lectures and group discussions devoted to specific problems in (1) research organization, (2) the administrative process, (3) research personnel, (4) aids to research, and (5) the research product. Program plans have been developed by a committee from the three participating institutions: M. H. Trytten and Raymund L. Zwemer, National Research Council; Howard A. Meyerhoff and S. B. Fracker, AAAS; Catheryn Seckler-Hudson, George P. Bush and Lowell

H. Hattery, The American University.

Inquiries about the Institute should be directed to Lowell H. Hattery, The American University, 1901 F Street, N.W., Washington 6, D. C.

**The American Academy of Neurology** will hold its first annual meeting in French Lick Springs, Indiana, June 1–3. A. B. Baker, professor of neurology, University of Minnesota, is president of the newly formed organization.

**The American Society for the Study of Sterility** will hold its fifth annual conference at the Hotel Strand, Atlantic City, New Jersey, June 6–7. The registration fee of $10 includes the detailed program containing abstracts of papers to be presented. Registration should be made in advance since seating capacity is limited. Address requests to Walter W. Williams, Secretary, 20 Magnolia Terrace, Springfield, Massachusetts.

**The Mathematical Association of America** will hold a joint meeting with the Mathematics Division of the American Society for Engineering Education June 20–21 at the Rensselaer Polytechnic Institute, Troy, New York. The association will also meet at the University of Colorado, Boulder, on August 29–30.

Centre National de la Recherche Scientifique has announced two forthcoming conferences: one on **morphogenesis**, to be held in Strasbourg, July 5–12, and one on **adsorption and heterogeneous kinetics**, to be held in Lyon, September 12–17. U. S. scientists invited to participate in the Strasbourg conference are: P. R. White, Institute for Cancer Research, Philadelphia; F. Skoog, University of Wisconsin, Madison; and P. Weiss, Department of Zoology, University of Chicago. Those who will take part in the Lyon conference are Hugh S. Taylor, of the Frick Chemical Laboratory, Princeton University, and Paul H. Emmett, Mellon Institute of Industrial Research, Pittsburgh.

**The International Union for the Scientific Study of Population** will hold its first official assembly since the war, in Geneva, Switzerland, August 27–September 3. At the request of Unesco, two special sessions of the assembly will be devoted to considering the cultural assimilation of immigrants. Further information regarding the assembly may be obtained from Frank Lorimer, Administrative Director, International Union for Scientific Study of Population, American University, Washington 16, D. C.

**The Mellon Institute and the University of Pittsburgh's School of Medicine** will hold their second annual symposium on orthopedic appliances at the institute September 19–24. The symposium will be open to invited orthopedic physicians, surgeons, and technologists. Inquiries concerning attendance and program should be addressed to the Orthopedic Appliance Fellowship, Mellon Institute, 4400 Fifth Avenue, Pittsburgh, Pennsylvania.

**The Southeastern Section of the American Physical Society** elected the following officers at its annual meeting held at Clemson Agricultural College, Clemson, South Carolina, April 15–16: J. H. Howey, Georgia Institute of Technology, Atlanta, chairman; W. G. Pollard, Oak Ridge Institute of Nuclear Studies, Oak Ridge, vice chairman; Dixon Callihan, Carbide and Carbon Chemicals Corporation, Oak Ridge, secretary; Hugh F. Henry, Carbide and Carbon Chemicals Corporation, treasurer; and Francis G. Slack, Vanderbilt University, member of the executive committee.

**The Wisconsin Academy of Sciences, Arts, and Letters** held its 79th annual meeting April 19–20 at the University of Wisconsin, as part of the university's centennial program. The following officers were elected for the 1949–50 academic year: Robert K. Richardson, professor of history and archivist, Beloit College, Beloit, president; Allen Abrams, Marathon Paper Company, Rothschild, vice president in science; Lucia R. Briggs, Milwaukee-Downer College, Milwaukee, vice president in arts; R. -M. S. Heffner, professor of German, University of Wisconsin, vice president in letters; H. O. Teisberg, State Historical Society, Madison, librarian; Banner Bill Morgan, associate professor of veterinary science, University of Wisconsin, secretary-treasurer.

## NRC News

The newly reorganized **Agricultural Board of the Division of Biology and Agriculture**, National Research Council, held its first meeting April 11 at the National Academy of Sciences. The Agricultural Board will be an independent scientific review body whose announced purposes are: to advance and interpret scientific knowledge pertaining to agriculture, to initiate and provide recommendations relative to agriculture, and to disseminate technical and deliberative conclusions among the proper agencies and population groups.

Roy C. Newton, director of research for Swift and Company, Chicago, is chairman of the new board. Leonard A. Maynard, director of the Cornell University School of Nutrition, is vice-chairman, and LeRoy Voris of the NRC Food and Nutrition Board is acting executive secretary. Other members are: R. V. Boucher, Pennsylvania State College; J. S. Davis, Food Research Institute of Stanford University; H. R. Guilbert, University of California; W. A. Hagan, New York State Veterinary College, Cornell University; W. E. Krauss, Agricultural Experiment Station, Wooster, Ohio; W. J. Loeffel, College of Agriculture, Nebraska; L. C. Norris, Cornell University; B. T. Simms, Bureau of Animal Industry, U. S. Department of Agriculture; and W. W. Spink, University of Minnesota Medical School. It is expected that several more members will be added to the board to insure balance in all agricultural fields.

The present committees of the Agricultural Board are on Animal Health; Public Health Aspects of Brucellosis; Animal Nutrition; Feed Composition; Production, Distribution, and Quality of Milk; and Veterinary Services. Most of the committees have been in existence and active for some time prior to the reorganization of the board. The Committee on Animal Nutrition and its subcommittees have published *Recommended Nutrient Allowances* for poultry, swine, dairy cattle, beef

cattle, and sheep; these have been widely accepted as standard and published in textbooks.

The Feed Composition Committee has recently made a survey of the nutritive value of hybrid corn, including vitamin, mineral, and proximate protein analyses. About 350 samples from different sources were investigated over a two-year period.

The Committee in Public Health Aspects of Brucellosis works in collaboration with the Division of Medical Sciences of the NRC. This committee, which estimates that brucellosis costs the livestock industry nearly $100 million annually, has published three reports on the disease, and is preparing definitive statements on the eradication of brucellosis in domestic animals and on the diagnosis of human brucellosis.

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**The Indiana Science Talent Search,** sponsored by the *Indianapolis Times,* the Indiana Academy of Science, and the Indiana Junior Academy of Science, honored 20 promising contenders for the Westinghouse Science Scholarships at the first Indiana Junior Scientists' Assembly, held in Indianapolis, March 26. The Indiana project is a part of the Eighth Annual Talent Search conducted by Science Clubs of America, a Science Service activity.

The 20 finalists, including the eight National Honorable Mentions, were interviewed during the morning by the talent search committee and in the afternoon exhibited the experimental equipment they had used in preparing their essays. Walter Leckrone, editor of the *Indianapolis Times,* presided at an Honors Luncheon, attended by more than 200 people. Karl Lark-Horovitz, head of the Department of Physics at Purdue University, addressed the group on "Science of the 20th Century." Mr. Leckrone presented awards to the 15 winners. All 20 students have been recommended to the entrance officials and scholarship committees of Indiana colleges and universities. Information on each of the 73 Indiana high school seniors who completed entrance requirements for the talent search was submitted to the college or university of his choice.

Members of the talent search committee are: R. W. Lefler, Department of Physics, Purdue University, Lafayette, chairman; Lawrence H. Baldinger, dean, College of Science, Notre Dame University; P. D. Edwards, Department of Mathematics, Ball State Teachers College, Muncie; Fernandus Payne, Department of Zoology and dean emeritus, Graduate School, Indiana University, Bloomington; and Winona H. Welch, Department of Botany, DePauw University, Greencastle. Ex-officio members are C. L. Porter, president of the Indiana Academy of Science, Department of Biology, Purdue University; H. H. Michaud, state sponsor, Indiana Junior Academy of Science, Department of Forestry, Purdue University; and Walter Leckrone, editor, *Indianapolis Times,* Indianapolis.

R. W. LEFLER.

**CARE, with the cooperation of Unesco,** plans to help rebuild war-damaged libraries of Europe and Asia by the distribution of free scientific and technical books. The program, to be in operation by May 15, 1950, will be financed entirely by voluntary subscriptions from American organizations and individuals on the same basis as the CARE food and clothing distribution system. Selection of books will be made by a group of American librarians headed by Luther Evans, Librarian of Congress. The books will be sent to Austria, Belgium, Czechoslovakia, Finland, Italy, France, Greece, Korea, Japan, Norway, Holland, Poland, Great Britain, Western Germany, and the whole of Berlin.

**The American Council of Learned Societies,** which at one time or another has organized such projects as the *Dictionary of American Biography* and the *Linguistic Atlas of the United States and Canada,* is now sponsoring, jointly with the Social Science Research Council, publication of a weekly *Current Digest of the Soviet Press.* Selected contents of 40-odd Russian periodicals are translated, condensed, arranged by subject matter, and indexed. The material is presented without comment or elaboration. The two most important newspapers, *Pravda* and *Izvestia,* are received by air mail and reported about three weeks after their Moscow publication. The yearly subscription rate is $150 and single copies are $3.00. Recognized scientific or educational bodies subscribing at the basic rate may obtain additional individual subscriptions, for their own use or for staff members, at a special rate of $25 each. Inquiries may be addressed to the *Current Digest of the Soviet Press,* 1219 Sixteenth Street, N. W., Washington 6, D. C.

## Recently Received—

Study Abroad: International Handbook of Fellowships, Scholarships and Educational Exchange, Vol. 1, 1948. Prepared by Unesco. Available through Publication Dept., Columbia University Press, New York 27, N. Y. at $1.00.

Dictionary of Guided Missile Terms: By the Committee on Guided Missiles of the Research and Development Board of the National Military Establishment. $1.00 paperbound, $2.00 clothbound from Public Affairs Press, Washington 8, D. C.

Radioautography by Tom McClure. In March 1949 issue of *Tracerlog,* issued by Tracerlab, 55 Oliver Street, Boston 10, Massachusetts.

Bibliography of Lobster Culture by Leslie W. Scattergood. Special scientific report 64, Fish and Wildlife Service, U. S. Dept. of Interior, Washington, D. C.

Prehistoric Art of the Aleutian Islands by George I. Quimby. *Fieldiana—Anthropology,* Vol. 36, No. 3. Available from Chicago Natural History Museum, Chicago, Illinois at $.30.

## Make Plans for—

**Society of American Bacteriologists,** 1949 annual meeting, May 16–20, Cincinnati, Ohio.

**American Society of Plant Physiologists,** New England section, May 20–21, University of New Hampshire, Durham.

**American Association of the History of Medicine,** annual meeting, May 23–24, Transylvania University, Lexington, Kentucky.